JOINT MEETING OF THE PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

8 AUGUST 2016

SPONSOR BRIEFING DOCUMENT

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Background

On 18 February 2016, Pfizer submitted to the United States (US) Food and Drug Administration (FDA) a supplemental New Drug Application requesting updates to the CHANTIX® (varenicline tartrate) Tablets labeling, relating to the risk of serious neuropsychiatric (NPS) adverse events (AEs) based on the outcomes of the postmarketing requirement (PMR) clinical study, which was specifically designed and conducted to assess this potential risk. The labeling updates proposed by Pfizer included removal of the Boxed Warning regarding serious NPS AEs, revisions to the corresponding Warnings and Precautions section based on the findings of this study, and inclusion of the study safety and efficacy outcomes in appropriate sections of the labeling. FDA subsequently scheduled a joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss this completed PMR study to determine whether the findings support changes to product labeling.

CHANTIX was approved by the US FDA in May 2006 as an aid to smoking cessation treatment for adults 18 and over. Within a year of approval, serious NPS AEs, including AEs related to suicide, began to be reported in the postmarketing experience. As this signal emerged in 2007 to 2008, warnings and precautions were added to the CHANTIX labeling to alert prescribers and patients to the potential risk of such events. In July 2009, a boxed warning regarding serious NPS AEs was added to the CHANTIX labeling, primarily on the basis of spontaneous postmarketing reports, to further highlight this safety information for prescribers.

At that time, there were no large, population-based observational studies published that analyzed the NPS safety of CHANTIX. FDA also indicated that the available clinical trial data were not adequate either to rule in or rule out an association between serious NPS AEs and the use of CHANTIX. FDA issued the PMR to Pfizer to conduct a "large randomized, double-blind, active- and placebo-controlled trial to compare the risk of clinically significant neuropsychiatric events, including but not limited to suicidality, in individuals using Chantix (varenicline), bupropion, nicotine replacement therapy, or placebo as aids to smoking cessation over 12 weeks of treatment, and to determine whether individuals with prior history of psychiatric disorders are at greater risk for development of clinically significant neuropsychiatric events compared to individuals without prior history of psychiatric disorders while using Chantix (varenicline) as an aid to smoking cessation. The trial should be sufficiently powered to adequately assess clinically significant neuropsychiatric events with each treatment and in both of the two subgroups (ie, with and without psychiatric disorders)." In parallel, a similar PMR was issued to GlaxoSmithKline (GSK) for its smoking cessation medication, bupropion (Zyban®), which has a diverse chemical structure and different mechanism of action than CHANTIX and for which serious NPS AEs were also reported. The EAGLES (**E**valuating **A**dverse Events in a **Gl**obal Smoking C**e**ssation **S**tudy) study was designed in consultation with FDA and conducted by Pfizer in collaboration with GSK to address the PMR.

EAGLES was a randomized, double-blind, triple-dummy, placebo- and active-controlled study, with 4 treatment arms, varenicline, bupropion, nicotine replacement therapy (NRT), and placebo. The NRT used in this study was a patch, available in the US over-the-counter (OTC), and served as an active comparator. Subjects were stratified into 2 cohorts, one including patients with a history of a psychiatric disorder and the other including subjects without a history of a psychiatric disorder. Mental health professionals (MHPs, defined as an MD or PhD psychologist) associated with every study site were responsible for confirming the Structured Clinical Interview for DSM-IV (SCID) psychiatric diagnoses and thus ensuring correct stratification to the non-psychiatric and psychiatric history cohorts. The MHPs were also responsible for evaluating AEs of interest associated with the primary endpoint and assuring subject safety. Measures were also in place to ensure that site personnel were qualified and adequately trained to carry out the study.

A primary composite NPS AE endpoint was developed specifically for the study to cover the spectrum of events reported in the postmarketing experience and reflected in the CHANTIX labeling. The endpoint included 16 components, each encompassing 1 or more individual AE terms. Severity criteria for the components of the composite endpoint were imposed to minimize inclusion of less clinically significant events, including some typically associated with nicotine withdrawal and thus increase the specificity of the endpoint. The primary safety endpoint was the occurrence of at least 1 treatment-emergent "severe" AE of anxiety, depression, feeling abnormal, or hostility, or at least 1 treatment-emergent "moderate" or "severe" AE of agitation, aggression, delusion, hallucination, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, or suicide. "Treatment-emergent" was defined as during treatment and up to 30 days after last dose of study medication.

The study included a variety of measures to enhance NPS AE collection and to capture secondary outcomes of interest. These measures included a structured Neuropsychiatric Adverse Event Interview (NAEI), proxy AE reporting by the subject's family and physicians, and use of validated psychiatric scales, including the Columbia Suicide Severity Rating Scale (C-SSRS), Hospital Anxiety and Depression Scale (HADS) and the Clinical Global Impression of Improvement (CGI-I) scale, which was directed to psychiatric status.

The study was designed as an estimation study due to its novel composite endpoint. The study was sized (1000 subjects per treatment arm per cohort) to provide sufficient precision to detect the NPS AE rate with an expected margin of error of ±1.9%, ±2.6%, and ±1.6% for the non-psychiatric cohort, the psychiatric cohort, and the overall study, respectively, for an attributable risk difference corresponding to an increase on a relative risk scale of 75% in the incidence of the endpoint versus placebo.

In April 2014, while EAGLES was still ongoing, Pfizer proposed revisions to the CHANTIX labeling based on the outcomes of 2 meta-analyses of randomized, placebo-controlled trials conducted by Pfizer and 4 large-scale, independent population-based observational studies comparing the NPS safety of CHANTIX to NRT and/or bupropion. The outcomes of these meta-analyses showed no increase in the incidence of suicidal ideation and/or behavior and a similar incidence of common psychiatric events in patients treated with CHANTIX compared to patients treated with placebo. The outcomes of the observational studies found that rates

of serious NPS AEs in patients taking CHANTIX did not differ from those taking NRT or bupropion, however, outcomes examined in these studies did not include the full range of NPS AEs that have been reported. These data were reflected in the CHANTIX label in September 2014.[1] In addition, in October 2014 FDA convened a joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss these data and a potential action for the boxed warning. The majority of committee members voted to "wait until the completion of the postmarketing randomized controlled trial to reassess the need for the boxed warning".

EAGLES has now been completed and the results were published in *The Lancet*.[2] In total, 8144 subjects were randomized (8058 of whom actually received study medication), with approximately equal numbers of subjects per cohort (~4000) and treatment group within cohort (~1000).

Safety Evaluation

The results of the primary NPS AE endpoint analysis showed a background rate of 3.7% in the placebo group overall across both cohorts and similar across treatment groups: varenicline 4.0%, bupropion 4.5%, and NRT 3.9%. In the non-psychiatric cohort, the observed rates of the composite primary NPS AE endpoint were: 1.3% in the varenicline treatment group, 2.2% in bupropion, 2.5% in NRT, and 2.4% in placebo. Not unexpectedly, the rates of the NPS AE endpoint were higher in the psychiatric cohort compared to the non-psychiatric cohort, but were similar across all treatment groups: 6.5% in varenicline, 6.7% in bupropion, 5.3% in NRT, and 4.9% in placebo.

In the non-psychiatric cohort, the risk difference (RD) and 95% confidence intervals (CIs) for the primary comparison of varenicline versus placebo were below zero, showing no increased risk of NPS AEs in the composite endpoint with varenicline treatment (-1.28 [-2.40, -0.15]). Similarly, the secondary pairwise comparisons including varenicline (varenicline vs NRT and varenicline vs bupropion) showed no increased risk of NPS events with varenicline, with RDs below zero and 95% CIs below or including zero.

In the psychiatric cohort, the primary comparison of varenicline versus placebo had RD above zero but 95% CIs including zero, showing no statistically significant increased risk of NPS AEs in the composite endpoint with varenicline treatment (1.59 [-0.42, 3.59]). Similarly, the secondary pairwise comparisons including varenicline (varenicline vs NRT and varenicline vs bupropion) also showed no statistically significant increased risk of NPS events, with 95% CIs including zero. The small numerical differences between the treatment groups were evaluated further in pre-specified secondary analyses and in additional post hoc exploratory analyses and reviews of subject level data.

The pre-specified secondary endpoint analyses of the composite NPS AE endpoint included analysis of the individual components of the endpoint and of the events that were rated as severe by Investigators. In both the non-psychiatric cohort and the psychiatric cohort, moderate or severe agitation was the most common component across all 4 treatment groups and was the only component of the 16 that occurred with sufficient frequency to allow statistical analysis. This analysis showed no significant differences between treatment

groups in either cohort. In the psychiatric cohort, Aggression was the component with the largest treatment differences between varenicline and placebo, and these differences were primarily in the Preferred Term (PT) Anger, which was reported by 0.8% of varenicline subjects compared to 0.4% of placebo subjects, 0.3% of NRT subjects and 0.2% of bupropion subjects. The occurrence of the NPS AE endpoint that were judged by the Investigator to be severe was low overall and the observed rates were similar across treatment groups in each cohort, particularly in the psychiatric cohort (1.4% in each active treatments and 1.3% for placebo).

A descriptive exploratory analysis was conducted, to ascertain whether the small numerical difference in the rates of the primary NPS AE composite endpoint seen in the varenicline versus placebo arms in the psychiatric cohort were driven by the AEs that were (1) rated as severe in intensity by Investigators (as discussed above), were SAEs by regulatory criteria (eg, events that result in death or are life threatening, lead to hospitalization (initial or prolonged), lead to a disability or permanent damage, require intervention to prevent permanent impairment or damage, or other - important medical events.), and (3) led to permanent treatment discontinuation. Both aggregate and patient level data were reviewed. The outcomes showed that the number of subjects with NPS AEs in these categories was low overall and generally similar for varenicline versus placebo, indicating that the small numerical difference in the rates of the primary NPS AE composite endpoint for varenicline versus placebo in the psychiatric cohort was not due to severe events, SAEs or events that led to permanent treatment discontinuation.

For NPS endpoint AEs that led to temporary or permanent discontinuation, the event outcomes were assessed to quantify the number of instances in which the event subsequently resolved, ie, positive dechallenge, which is a phenomenon observed in some postmarketing cases. The presence of positive dechallenge outcomes in the placebo treatment group in greater numbers to those reported for varenicline suggests that these events may be episodic in nature and not related to study treatment. This observation illustrates the difficulty in interpreting similar events in the postmarketing setting and suggests that the use of dechallenge outcomes in ascertainment of causality in postmarketing experience for NPS events is questionable.

The C-SSRS provided additional data for the evaluation of suicide-related events. The percentage of subjects with suicidal ideation and/or behavior based on the C-SSRS was similar across all treatment arms in both the non-psychiatric and psychiatric cohorts during treatment. The rates were higher in the psychiatric cohort compared to the non-psychiatric cohort for all treatments. The single completed suicide during the study was committed by a subject in the non-psychiatric cohort treated with placebo.

Two additional structured assessments were also administered during the study to further evaluate psychiatric status: the HADS and the CGI-I scale. Mean scores from the HADS and CGI-I were very similar across treatment arms and showed no change or slight improvement over the course of the study in both cohorts. The results of these assessments supported the conclusion of no increased risk of NPS events with varenicline treatment observed in this study.

Efficacy Evaluation

The primary focus of EAGLES was NPS safety; however, the study also included efficacy assessments as main objectives, and the triple-dummy design of the study allowed direct comparison of the active treatments as well as standard comparisons to placebo. Efficacy results showed that all 3 active treatments had higher efficacy rates than placebo and demonstrated superior abstinence rates for varenicline compared to placebo, as well as compared to bupropion and NRT, both in subjects with and those without a psychiatric history. This was the first placebo-controlled clinical trial to directly compare the 3 pharmacotherapies and it confirmed CHANTIX as the most effective smoking cessation therapy among these 3 treatments for adult smokers who are motivated to quit.

Conclusions

In conclusion, as presented in this Briefing Document, EAGLES was specifically designed and conducted using a composite NPS AE endpoint to evaluate the concerns raised by postmarketing reports regarding the NPS safety of CHANTIX, and the outcomes showed no increased risk of serious NPS AEs with varenicline treatment compared to placebo, or compared with NRT patch (OTC smoking cessation medication), regardless of a subject's psychiatric history. The study outcomes also showed that serious NPS AEs occur in subjects attempting to quit smoking regardless of smoking cessation treatment. Serious NPS AEs that were reported for subjects taking placebo in both cohorts were not unlike those reported for varenicline in postmarketing experience, as far as general types of AEs reported, as well as the presence of cases of positive dechallenge, in which AEs resolved after discontinuation of placebo. In the psychiatric cohort, a small numerical increase in the incidence of the composite endpoint in varenicline versus placebo was observed but was not driven by events that were serious or severe or that led to treatment discontinuation.

These safety data from EAGLES, combined with efficacy outcomes aid to the understanding of the benefit risk profile of varenicline. Specifically, the safety data from EAGLES build on and help address the limitations of the previously conducted meta-analyses of randomized clinical trials and large observational studies, and provides a better understanding of the nature of serious NPS AEs reported in postmarketing experience. In its totality, the accumulated body of scientific evidence on the NPS safety of CHANTIX does not support an increased risk of serious NPS AEs with CHANTIX treatment. Therefore, these collective data indicate that the potential risk of serious NPS AEs with varenicline use is substantially lower than is conveyed in the currently approved CHANTIX labeling. With respect to efficacy, EAGLES confirmed varenicline as the most effective monotherapy treatment option currently available for smokers who want to quit. The health benefits of quitting smoking have been firmly established. Smoking cessation is among the most valuable of public health measures and continues to be of urgent importance. In this context, CHANTIX is an important smoking cessation treatment option for patients who want to quit.

Timely communication of the newly acquired data is important and product labeling should accurately reflect the product safety and efficacy profile in order for patients and prescribers to make informed decisions about treatment. Based on the totality of scientific evidence available to date, including the safety and efficacy outcomes of EAGLES, Pfizer believes

that the boxed warning regarding reports of serious NPS adverse events in patients attempting to quit smoking with CHANTIX as currently included in the CHANTIX label, does not accurately reflect the NPS safety profile of CHANTIX and should be removed as it has the potential to deter appropriate use of CHANTIX.

Nevertheless, given that serious NPS AEs have been reported in the postmarketing experience in patients attempting to quit smoking with CHANTIX, and acknowledging that controlled clinical trials may not be able to completely rule out very rare or idiosyncratic events, Pfizer proposes to retain the WARNINGS and PRECAUTIONS section of the label regarding NPS events occurring in patients attempting to quit smoking and also include the information regarding NPS events from the EAGLES trial in this section. Pfizer believes that such warning sufficiently alerts prescribers to the possibility that these types of events may occur in smokers attempting to quit.

1 CHANTIX [US Package Insert]. New York, NY: Pfizer Inc; 2014.

2 Anthenelli RA, Benowitz NL, West R, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomized, placebo-controlled clinical trial. Lancet 2016;387:2507-20.

LIST OF ABBREVIATIONS

AE	Adverse event
B	Bupropion
BID	Twice daily
CA	Continuous abstinence
CAR	Continuous abstinence rate
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
CI	Confidence interval
CO	Carbon monoxide
COPD	Chronic obstructive pulmonary disease
Cred I	Credibile interval
C-SSRS	Columbia Suicide Severity Rating Scale
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders 4th Edition Text Revision
EAGLES	**E**valuating **A**dverse Events in a **Gl**obal Smoking C**e**ssation **S**tudy
GSK	GlaxoSmithKline
FDA	Food and Drug Administration
FTND	Fagerström Test for Nicotine Dependence
HADS	Hospital Anxiety and Depression Scale
HAM-D	Hamilton Depression Rating Scale
HLGT	(MedDRA) High Level Group Term
HR	Hazard ratio
IDMC	Independent Data Monitoring Committee
IP	Investigational product
Max	Maximum
MDD	Major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MHP	Mental health professional
MNWS	Minnesota Nicotine Withdrawal Scale
Min	Minimum
N	Total number
n	Number with observation of interest
NAEI	Neuropsychiatric Adverse Event Interview
NEC	Not elsewhere classified
NPS	Neuropsychiatric
NRT or N (in forest plots)	Nicotine replacement therapy
NUI	Nicotine Use Inventory
OR	Odds ratio
OTC	Over-the-counter
OTIS	Off Treatment and In Study
PANSS	Positive and Negative Syndrome Scale
Pbo or P	Placebo
PD	Protocol deviation
PHQ	Patient Health Questionnaire

PHx	Psychiatric history
PMR	Postmarketing Requirement
PT	(MedDRA) Preferred Term
QD	Once daily
RD	Risk difference
RTC	Randomized controlled trial
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SANS	Scale for the Assessment of Negative Symptoms
SCID I-II	Structured Clinical Interview for DSM-IV Axis I-II Disorders
SD	Standard deviation
SR	Sustained release
TQD	Target quit date
US	United States
USPI	United States Package Insert
Var or V	Varenicline
v	version
vs	versus
W or Wk	Week

1. BACKGROUND

1.1. Introduction

This Briefing Document provides background information for the joint Psychopharmacologic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee meeting and is focused on describing the design and results of Post Marketing Requirement (PMR) study referred to as EAGLES (**E**valuating **A**dverse Events in a **Gl**obal Smoking C**e**ssation **S**tudy). The results of the study are put into the context of the large body of accumulated data on neuropsychiatric (NPS) adverse events (AEs) and the use of varenicline as an aid to smoking cessation treatment to support proposed label changes, which include removal of the boxed warning and retention of the WARNINGS and PRECAUTIONS section of the label regarding NPS events occurring in patients attempting to quit smoking and inclusion of the information regarding NPS events from the EAGLES trial in this section.

1.2. Regulatory History Regarding Neuropsychiatric Events

CHANTIX was approved by the United States Food and Drug Administration (FDA) in May 2006 as an aid to smoking cessation treatment for adults 18 and over. Within a year of approval, serious NPS AEs, including AEs related to suicide, began to be reported in the postmarketing experience. As this signal emerged in 2007 to 2008, warnings and precautions were added to the CHANTIX labeling to alert prescribers and patients to the potential risk of such events. In July 2009, a boxed warning regarding serious NPS AEs was added to the CHANTIX labeling, primarily on the basis of spontaneous postmarketing reports, to further highlight this safety information for prescribers.

The boxed warning agreed upon by the Agency and Pfizer in July 2009 is shown below.[3] The same information was also reflected in the WARNINGS section of the label under the subheading Neuropsychiatric Symptoms and Suicidality.

> Serious neuropsychiatric events including, but not limited to, depression, suicidal ideation, suicide attempt, and completed suicide have been reported in patients taking CHANTIX. Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking CHANTIX who continued to smoke.
> All patients being treated with CHANTIX should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide. These symptoms, as well as worsening of pre-existing psychiatric illness and completed suicide, have been reported in some patients attempting to quit smoking while taking CHANTIX in the postmarketing experience. When symptoms were reported, most were during CHANTIX treatment, but some were following discontinuation of CHANTIX therapy.

These events have occurred in patients with and without pre-existing psychiatric disease. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the premarketing studies of CHANTIX, and the safety and efficacy of CHANTIX in such patients has not been established.
Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many postmarketing cases, resolution of symptoms after discontinuation of CHANTIX was reported, although in some cases the symptoms persisted; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.
The risks of CHANTIX should be weighed against the benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial.

(See **WARNINGS/Neuropsychiatric Symptoms and Suicidality, PRECAUTIONS/Information for Patients, and ADVERSE REACTIONS/Post-Marketing Experience**)

At that time, FDA noted that available clinical trial data was not sufficient to rule in or rule out an association between these serious NPS AEs and varenicline treatment and it was acknowledged by FDA that an analysis of spontaneous postmarketing AEs in FDA's pharmacovigilance systems would not be sufficient to assess the known serious risk of NPS AEs with varenicline treatment. Pfizer was issued a PMR to conduct a large randomized, double-blind, active- and placebo-controlled study to compare the risk of clinically significant NPS events, including but not limited to events related to suicidality, in individuals using varenicline, bupropion, nicotine replacement therapy (NRT), or placebo as aids to smoking cessation, and to determine whether individuals with a history of psychiatric disorders are at greater risk for development of clinically significant NPS AEs compared to smokers without a history of psychiatric disorders, while using varenicline as an aid to smoking cessation (see Section 2.1.1 for additional specifications of the PMR). FDA also requested a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of varenicline outweigh the risks. At the same time, FDA issued a similar PMR to GlaxoSmithKline (GSK) for its smoking cessation medication, bupropion, which has a different mechanism of action and diverse chemical structure than CHANTIX and for which serious NPS AEs were also reported. A single PMR study was ultimately conducted by Pfizer in collaboration with GSK.

In April 2014, while EAGLES was still ongoing, Pfizer proposed revisions to the CHANTIX labeling based on the outcomes 2 meta-analyses of randomized, placebo-controlled trials conducted by Pfizer and 4 large-scale, population-based observational studies comparing the neuropsychiatric safety of CHANTIX to NRT and/or bupropion. The outcomes of these meta-analyses showed no increase in the incidence of suicidal ideation and/or behavior and a similar incidence of common psychiatric events in patients treated with CHANTIX compared

to patients treated with placebo. The outcomes of the observational studies found that rates of serious NPS AEs in patients taking CHANTIX did not differ from those taking NRT or bupropion, however, outcomes examined in these studies did not include the full range of NPS AEs that have been reported. These data were reflected in the CHANTIX label in September 2014 as shown below.[4] The data are located in the WARNINGS AND PRECAUTIONS section of the currently approved CHANTIX label under the subheading Neuropsychiatric symptoms and suicidality.

Since the initial signal of neuropsychiatric symptoms and suicidality emerged, additional analyses and studies have been conducted to further evaluate this association.

Analyses of clinical trials

A meta-analysis of 5 randomized, double blind, placebo controlled trials, including 1907 patients (1130 CHANTIX, 777 placebo) was conducted to assess suicidal ideation and behavior as reported on the Columbia-Suicide Severity Rating Scale (C SSRS). This meta-analysis included one trial (N=127) in patients with a history of schizophrenia or schizoaffective disorder and another trial (N=525) in patients with a history of depression. The results showed no increase in the incidence of suicidal ideation and/or behavior in patients treated with CHANTIX compared to patients treated with placebo, with a Risk Ratio (RR) of 0.79 (95% Confidence Interval [CI]: 0.46, 1.36), as shown in Table 1. Forty-eight (48) of the 55 patients who reported suicidal ideation or behavior (24 CHANTIX, 24 placebo) were observed in the two trials that enrolled patients with a history of schizophrenia, schizoaffective disorder, or depression. Few events were observed in the other three trials (4 CHANTIX, 3 placebo).

Table 1. Number of Patients and Risk Ratio for Suicidal Ideation and/or Behavior Reported on C-SSRS from a Meta-Analysis of 5 Clinical Trials Comparing CHANTIX to Placebo

	CHANTIX (N=1130)	**Placebo** (N=777)
Patients with Suicidal ideation and/or behavior* [n (%)]**	28 (2.5)	27 (3.5)
Patient-years of exposure	325	217
Risk Ratio # (RR; 95% CI)	0.79 (0.46, 1.36)	

* Of the events, one patient in each treatment arm reported suicidal behavior
** Patients with events **up to 30 days after treatment**; % are not weighted by study
# RR of incidence rates per 100 patient years

A pooled analysis of 18 double-blind, randomized, placebo-controlled clinical trials, which includes the 5 trials that collected C-SSRS described in Table 1, was conducted to assess the psychiatric safety of CHANTIX. This pooled analysis included 8521 patients (5072 CHANTIX, 3449 placebo), some of whom had psychiatric conditions at baseline. Table 2 describes the most frequently (≥ 1%) reported adverse events related to psychiatric safety. The results showed a similar incidence of common psychiatric events in patients treated with CHANTIX compared to patients treated with placebo.

Table 2. Psychiatric Adverse Events Occurring in ≥ 1% of Patients from Pooled Analysis of 18 Clinical Trials

	CHANTIX (N=5072)	**Placebo** (N=3449)
Anxiety disorders and symptoms	253 (5.0)	206 (6.0)
Depressed mood disorders and	179 (3.5)	108 (3.1)

disturbances		
Mood disorders and disturbances NEC*	116 (2.3)	53 (1.5)

* NEC = Not Elsewhere Classified
Counts (percentages) corresponds to the number of patients reporting the event

Observational Studies

Four observational studies, each including 10,000 to 30,000 users of CHANTIX in the adjusted analyses, compared the risk of selected serious neuropsychiatric events (neuropsychiatric hospitalizations, fatal and non-fatal self-harm), between CHANTIX users and prescription NRT or bupropion users. All studies were retrospective cohort studies and included patients with and without a psychiatric history.

Two of the studies found no difference in risk of neuropsychiatric hospitalizations between CHANTIX users and nicotine patch users (Hazard Ratio [HR] 1.14; 95% Confidence Interval [CI]: 0.56–2.34 in the first study, and 0.76; 95% CI: 0.40-1.46 in the second study). However, neither study validated the diagnostic codes used to identify outcomes against medical records. A third study reported no difference in risk of psychiatric adverse events diagnosed during an emergency department visit or inpatient admission between CHANTIX users and bupropion users (HR 0.85; 95% CI: 0.55-1.30). Bupropion has also been associated with neuropsychiatric adverse events. A fourth study examined risk of fatal and non-fatal self-harm in users of CHANTIX compared to users of NRT. Although the occurrence of detected suicide was rare during the three months after patients initiated any drug treatment (two cases in 31,260 CHANTIX users and six cases in 81,545 NRT users), this study has important limitations. Most importantly, these data were captured following public awareness of reports of neuropsychiatric adverse events in CHANTIX users. CHANTIX users had fewer comorbid conditions that could put them at risk for neuropsychiatric adverse events, suggesting that patients with a history of neuropsychiatric illness were preferentially prescribed NRT, and healthier patients were preferentially prescribed CHANTIX.

Outcomes examined in these studies did not include the full range of neuropsychiatric adverse events that have been reported.

In October 2014, FDA convened a joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss these data and a potential action for the boxed warning. The majority of committee members voted to "wait until the completion of the postmarketing randomized controlled trial to reassess the need for the boxed warning". FDA also stated, "there is no specific regulation or guidance that has been established to remove a boxed warning" and that "however, if the criteria for including a boxed warning are no longer met, it is reasonable to remove it."

EAGLES has now completed and on 16 November 2015, Pfizer submitted to FDA the Clinical Study Report (CSR) for the study, Pfizer study number A3051123, *A Phase 4, Randomized, Double Blind, Active And Placebo Controlled, Multicenter Study Evaluating the Neuropsychiatric Safety and Efficacy of 12 Weeks Varenicline Tartrate 1 mg BID and Bupropion Hydrochloride 150 mg BID for Smoking Cessation in Subjects With and Without a History of Psychiatric Disorders*. On 18 February 2016, Pfizer submitted to FDA a supplemental New Drug Application (sNDA) for proposed label changes based on the study, including removal of the Boxed Warning on serious neuropsychiatric events, revisions to the corresponding Warnings and Precautions section, and inclusion of the study safety and efficacy outcomes in appropriate sections of the labeling. FDA consequently scheduled a joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety

and Risk Management Advisory Committee to discuss the completed PMR along with relevant published observational studies to determine whether the outcomes support changes to product labeling.

The study will be described in detail in the Section 2; however, an understanding of the health consequences of smoking and the importance of smoking cessation, which is discussed briefly below, is important for consideration of the results.

1.3. Importance of Smoking Cessation Therapies: Health Burden of Smoking

The importance of making available effective smoking cessation therapies is underscored by the health burden caused by smoking. Risks associated with smoking cessation pharmacotherapies need to be considered in conjunction with the benefits of quitting smoking.

The health effects of smoking are well characterized and far reaching, and smoking remains the leading cause of preventable death and disease in the US.[5] The Centers for Disease Control and Prevention (CDC) fact sheet on the health effects of smoking[6] includes the following:

- Cigarette smoking causes more than 480,000 deaths each year in the United States. This is nearly one in five deaths. (A recent report suggests this number may actually be higher.[7])
- Smoking causes about 90% of all lung cancer deaths in men and women.
- About 80% of all deaths from chronic obstructive pulmonary disease (COPD) are caused by smoking.
- Smoking is estimated to increase the risk:
  - For coronary heart disease by 2 to 4 times,
  - For stroke by 2 to 4 times,
  - Of men developing lung cancer by 25 times, and
  - Of women developing lung cancer by 25.7 times.
- Smokers are 12 to 13 times more likely to die from COPD than nonsmokers.
- Smoking increases the risk for cancer throughout the body.
- Smoking reduces fertility and increases risks for:
  - Preterm (early) delivery,
  - Stillbirth (death of the baby before birth),
  - Low birth weight,
  - Sudden infant death syndrome (known as SIDS or crib death),
  - Ectopic pregnancy, and

- Orofacial clefts in infants.

- Smoking affects the health of teeth and gums and can cause tooth loss.
- Smoking can increase the risk for cataracts and age-related macular degeneration.
- Smoking is a cause of type 2 diabetes mellitus and can make it harder to control. The risk of developing diabetes is 30–40% higher for active smokers than nonsmokers.
- Smoking causes general adverse effects on the body, including inflammation and decreased immune function.
- Smoking is a cause of rheumatoid arthritis.

The health benefits of quitting smoking are also well established[8] and include:

- Lowered risk for lung cancer and many other types of cancer.
- Reduced risk for heart disease, stroke, and peripheral vascular disease.
- Reduced respiratory symptoms.
- Reduced risk of developing COPD.
- Reduced risk for infertility in women of childbearing age.

1.4. Prevalence of Smoking in the United States

The prevalence of current cigarette smoking among US adults reached a low of 15.2% in 2015, an almost 10% drop from the 24.7% reported in 1997.[9] Despite the decline in the percent of adult smokers, the absolute number of smokers remains high; approximately 40 million adults[5]. Smoking is prevalent across all adult demographic groups in the US, including those defined by age, gender, race/ethnicity, education and economic status.[10]

People with mental illness comprise a large section of the smoking population. People with mental illness smoke at a 70% higher rate than adults without mental illness (36% and 21%, respectively).[11,12] Nearly 1 in 5 adults in the US –about 45.7 million- have some type of mental illness yet those with a mental illness smoke almost one-third of all cigarettes.[13] While the proportion of current smokers has declined substantially among people with no or low levels of psychological distress, the decline has been lower among people with high levels of psychological distress.[14] These smoking rates underlie a growing mortality disparity between those with and without serious mental illness; smokers with chronic mental illnesses die up to 25 years earlier than the general population.[15] Previous perceptions were that smokers with mental illnesses do not want to quit and that quitting would exacerbate their underlying disease.[16,17] More recent research has shown these perceptions to be false.[18,19] Torres et al.[20] found that in smokers using an online self-help program, quitting smoking was not associated with an increase in major depressive episodes. They reported that abstaining from smoking did not increase the risk of major depressive episodes in those with a history of depression relative to those with no history of depression, although a history of depression was itself a predictor of major depressive episodes in smokers. Furthermore, not quitting was associated with increased major depressive episodes shortly following a quit attempt. Two other studies,[21,22] using different methodologies also failed to show an increase

in depressive episodes with abstinence in smokers with or without a history of depression. Smokers with mental illness are as likely to want to quit smoking as the general population,[23] but often do not receive help.[24,25,26] Smokers with mental illness can successfully quit smoking and abstinence from smoking can actually be associated with improved mental health.[27,28] One conclusion from these data is that smokers with mental illness are an important population to include for smoking cessation efforts.

Considering the health harms of smoking and the prevalence in the US population, smoking cessation is a public health effort with high value and making available products that increase the probability of successfully quitting smoking is one measure that can be taken.

Of note, that there have been no new smoking cessations approved since varenicline in 2006 and currently there are only 3 FDA approved cessation medications (varenicline, bupropion and various forms of NRT).

2. EAGLES

2.1. Study Design

2.1.1. Objectives

FDA's stated goal for the PMR was[29]: "*A large randomized, double-blind, active- and placebo-controlled trial to compare the risk of clinically significant neuropsychiatric events, including but not limited to suicidality, in individuals using Chantix (varenicline), bupropion, nicotine replacement therapy, or placebo as aids to smoking cessation over 12 weeks of treatment, and to determine whether individuals with prior history of psychiatric disorders are at greater risk for development of clinically significant neuropsychiatric events compared to individuals without prior history of psychiatric disorders while using Chantix (varenicline) as an aid to smoking cessation. The trial should be sufficiently powered to adequately assess clinically significant neuropsychiatric events with each treatment and in both of the two subgroups (i.e., with and without psychiatric disorders).*"

With this in mind, EAGLES was designed primarily as a safety study, although the large sample size allowed for a robust evaluation of comparative efficacy. The study, as described in more detail in the following sections, was a randomized, double-blind, placebo- and active-controlled, parallel group, multi-center, multi-country study, with 4 treatment groups and 2 cohorts and a 12 week treatment period followed by 12 weeks of non-treatment follow-up (24 weeks total). Aspects of the study design, including the primary endpoint, were discussed and agreed upon with FDA and the protocol was considered acceptable by the agency.[29] GSK collaborated with Pfizer in the planning and execution of the study.

2.1.2. Treatment Groups

Study subjects were randomly assigned to 1 of 4 treatment arms (1:1:1:1): varenicline 1 mg twice daily (BID), bupropion sustained release (SR) 150 mg BID, NRT patch 21 mg daily (with a taper to 7 mg daily), or placebo. The dosing regimen for each drug was based on the approved/labelled dosing at the time the study initiated. The study used a triple dummy design meaning that each participant received 3 treatments; for those in an active treatment arm (varenicline, bupropion, and NRT), the treatment they were assigned to was active and

the other 2 treatments were matched placebos, and for those in the placebo group, all 3 treatments were matched placebos. All subjects were instructed to set their target quit date as 1 week after the start of the study. Varenicline and bupropion (and their matching placebos) were initiated on Study Day 1, 1 week prior to the target quit date and the NRT patch (and its matching placebo) was initiated on the target quit date (Day 8). Details of the dosing regimen for each treatment arm are provided in Table 1.

Table 1. EAGLES Treatment Administration and Dosing Schedule

Treatment Group	Days 1-3	Days 4-7	Weeks 1[a]-8	Weeks 8-10	Weeks 10-12
Varenicline	0.5 mg V QD 1 pbo B QD	0.5 mg V BID 1 pbo B BID	1 mg V BID 1 pbo B BID 1 pbo NRT QD	1 mg V BID 1 pbo B BID 1 pbo NRT QD	1 mg V BID 1 pbo B BID 1 pbo NRT QD
Bupropion	150 mg B QD 1 pbo V QD	150 mg B BID 1 pbo V BID	150 mg B BID 1 pbo V BID 1 pbo NRT QD	150 mg B BID 1 pbo V BID 1 pbo NRT QD	150 mg B BID 1 pbo V BID 1 pbo NRT QD
NRT patch	1 pbo V QD 1 pbo B QD	1 pbo V BID 1 pbo B BID	21 mg NRT QD 1 pbo V BID 1 pbo B BID	14 mg NRT QD 1 pbo V BID 1 pbo B BID	7 mg NRT QD 1 pbo V BID 1 pbo B BID
Placebo	1 pbo V QD 1 pbo B QD	1 pbo V BID 1 pbo B BID	1 pbo V BID 1 pbo B BID 1 pbo NRT QD	1 pbo V BID 1 pbo B BID 1 pbo NRT QD	1 pbo V BID 1 pbo B BID 1 pbo NRT QD

a. At the Week 1 visit, the varenicline dose was to be taken as 2 × 0.5 mg tablets (or 2 placebo varenicline tablets) in the AM and 1 mg tablet (or 1 placebo varenicline tablet) in the PM.
B=bupropion; BID=twice daily; NRT=nicotine replacement therapy; QD=once daily; V=varenicline; pbo=placebo.

To address FDA concerns about differential risk of serious NPS AEs in subjects with or without a history of a psychiatric disorder, subjects were stratified into 1 of 2 cohorts, those with a diagnosed history (current and/or past) of a psychiatric disorder (referred to as the "PHx cohort") and those without a history of a psychiatric disorder (referred to as the "non-PHx cohort"). Cohort stratification was confirmed by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders 4th Edition-Text Revision (DSM-IV-TR) Axis I and II disorders (SCID I and II), which was conducted at the screening visit by trained site personnel. Additional steps to ensure proper stratification were taken:

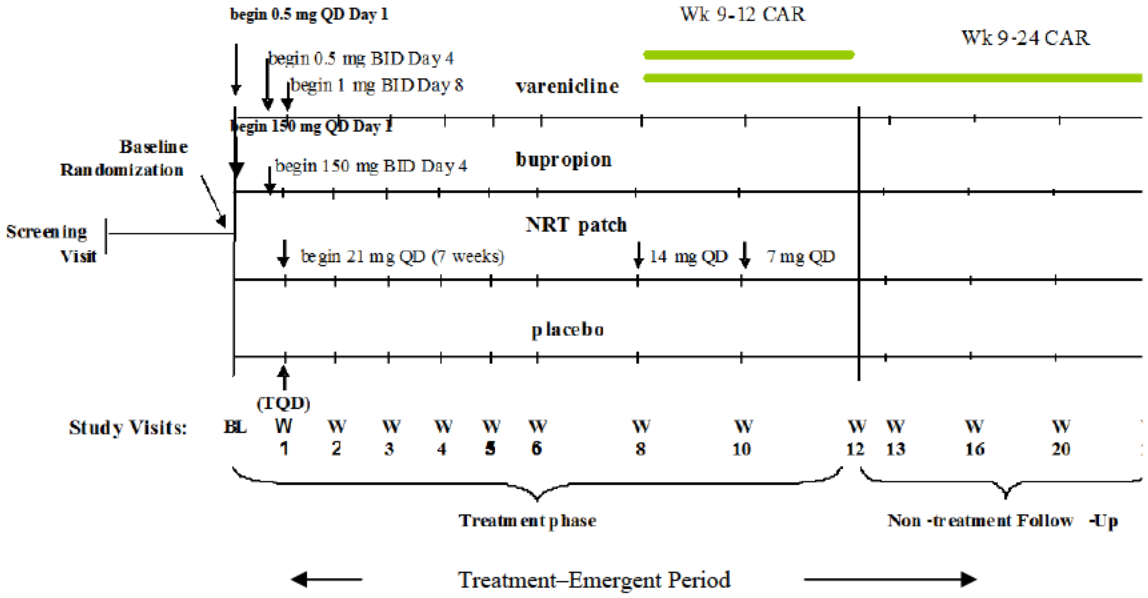
- Qualifications for site personnel administering the SCID were defined: clinician or qualified person trained in clinical mental health (ie, PhD level clinical psychologist or masters level training in related areas (psychologist, social work)
- Site personnel were trained on completing the SCID by an external vendor (Worldwide Clinical Trials (WCT), Inc) and were required to complete SCID refresher training every 6 months while subjects were being screened
- For subjects determined to have a psychiatric disorder, SCID diagnoses were confirmed by a qualified mental health professional (MHP), defined as a psychiatrist or licensed PhD level psychologist.

Subjects in the PHx cohort were further stratified based on which of 4 categories their primary diagnosis was in: mood disorders, anxiety disorders, psychotic disorders, or personality disorders. These categories were also agreed upon with FDA. Further details about the psychiatric diagnoses are provided in Section 2.1.4.2 below.

2.1.3. Study Procedures

The study design included a 12-week treatment phase followed by a 12-week non-treatment follow-up phase, for a total study duration of 24 weeks. Subjects were instructed to quit smoking 1 week after starting treatment, which coincided with the end of titration period for varenicline and bupropion and the initiation of NRT treatment (see Table 1). Figure 1 shows a schematic diagram of the study. Subjects had in-clinic visits in Weeks 1-6, and Weeks 8, 10, 12, 13, 16, 20, and 24. Subjects were contacted by telephone during the in-between weeks. Volunteered AEs were captured at both in-clinic visits and telephone contacts, while solicited AEs (using a structured interview) were captured only at in-clinic visits and psychiatric scales, as described in more detail below, were also administered at in-clinic visits. In addition, counseling for smoking cessation (10 minutes or less) was provided at each in-clinic visit. Smoking status was assessed at in-clinic visits and during telephone contacts.

Figure 1. Study A3051123 Study Design and Plan



BID=twice daily; BL=baseline; CAR=continuous abstinence rate; QD=once daily; TQD=target quit date; W or Wk=week; NRT=nicotine replacement therapy.

2.1.4. Inclusion/Exclusion Criteria

2.1.4.1. General inclusion/exclusion criteria

All subjects, regardless of cohort, had to meet the general study enrollment criteria.

Some of the general inclusion criteria of specific importance to the study were:

- Male or female cigarette smokers, 18-75 years of age, motivated to stop smoking and considered suitable for a smoking cessation attempt.

- Smoked an average of at least 10 cigarettes per day during the past year and during the month prior to the screening visit, and had an exhaled CO >10 parts per million (ppm) at screening.

Some of the general exclusion criteria of specific importance to the study were:

- Subjects with an Axis I diagnosis according to DSM-IV-TR criteria who had a rating of 5 or higher on the Clinical Global Impression of Severity (CGI-S).

- Subjects who were believed to have a suicidal risk at screening, baseline, or after assessment by a qualified MHP if a risk assessment interview was required after screening or baseline based on positive responses on the Columbia Suicide Severity Rating Scale (C-SSRS).

    - Suicidal ideation associated with actual intent and/or plan in the past year: Yes answer on item 5 of the C-SSRS.
    - Previous history of suicidal behaviours in the past year.

- Subjects who had taken varenicline, bupropion, or NRT within 30 days prior to baseline visit.

- Subjects for whom treatment with bupropion was not appropriate:

    - Subjects with a current seizure disorder or any history of seizures;
    - Subjects undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines);
    - Subjects with current or prior diagnosis of anorexia or bulimia nervosa;
    - Subjects who had taken a monoamine oxidase inhibitor within the past 14 days (prior to the baseline visit);
    - Subjects who were taking the following narrow therapeutic range medications that are metabolised by cytochrome P450 (CYP) 2D6: desipramine, nortriptyline, Type 1C anti-arrhythmics (eg, propafenone, flecainide), and thioridazine.

- Subjects who did not agree to abstain from using non-cigarette tobacco products (including pipe tobacco, cigars, snuff, chewing tobacco, hookah, etc) or marijuana during study participation.

- Subjects who did not agree to abstain from using NRT, bupropion, varenicline, and other aids to smoking cessation during study participation (both the treatment phase

and the post-treatment follow-up). [Note that although this was considered a protocol deviation and use of such products was captured as concomitant medications, subjects could remain in the study.]

- Subjects with skin conditions resulting in red, broken, or irritated skin that could hinder the use of the NRT patch.

2.1.4.2. Psychiatric History Cohort Inclusion/Exclusion Criteria

A noted above, there were 2 cohorts of subjects, those with a diagnosed history (current and/or past) of a psychiatric disorder and those without a history of a psychiatric disorder, as confirmed by the SCID, conducted at the screening visit. For the purposes of this study, a "current" diagnosis was defined as meeting the established criteria in the prior month and a "past" or "lifetime" diagnosis was defined as meeting the established criteria anytime in the past medical history. Subjects were included in the PHx cohort if they had a primary diagnosis of 1 of the following 4 types of DSM-IV-TR Axis I and II disorders (as discussed and agreed upon with FDA) and they were considered clinically stable (no acute exacerbation of their condition in past 6 months, if on medication, stable drug and dose ≥3 months, no change in treatment anticipated, not at high risk of self-injury or suicidal behaviour):

- Psychotic disorders limited to schizophrenia and schizoaffective disorder
- Mood disorders limited to major depression, bipolar I and bipolar II disorders (with the exception of European countries where bipolar disorders were excluded due to bupropion labelling)
- Anxiety disorders limited to panic disorder with or without agoraphobia, post-traumatic stress disorder, obsessive-compulsive disorder, social phobia, and generalised anxiety disorder
- Personality disorders limited to borderline personality disorder (past history)

The psychiatric disorders listed below were considered exclusionary for study enrollment, if any 1 of them was the subject's sole current or past diagnosis. However, if a subject had a primary diagnosis of 1 of the inclusionary disorders above, they could still be enrolled if the subject was able to comply with all study requirements. In addition, subjects with past substance abuse/misuse had to be in full remission for 12 months and not taking opioid agonists or partial agonists. If subjects had current co-morbid conditions other than those listed below, they could be considered for enrollment after consultation with a medical monitor.

- Psychotic disorders including schizophreniform disorder, delusional disorder, and psychotic disorders not otherwise specified
- All delirium, dementia, and amnestic and other cognitive disorders
- All substance-induced disorders (other than nicotine)
- All factitious disorders

- All dissociative disorders
- All impulse control disorders
- Evidence of substance abuse/misuse or dependence severe enough to compromise the subject's ability to comply with the study requirements;
- Subjects with antisocial, schizotypal, or any other personality disorder severe enough to compromise the subject's ability to comply with the study requirements.

Psychiatric history cohort eligibility criteria for each subject were reviewed by WCT prior to subject enrollment.

2.1.4.3. Non-Psychiatric History Cohort Inclusion/Exclusion Criteria

To be included in the non-PHx cohort, subjects could not have had a diagnosis of any type of psychiatric disorder confirmed by the SCID administered at the screening visit (as a primary or comorbid diagnosis in the past or currently, including substance use disorders). Non-psychiatric history cohort eligibility criteria for each subject were reviewed by WCT prior to subject enrollment.

2.1.5. Enhanced Neuropsychiatric Assessment Procedures

The EAGLES study design included several procedures to help ensure robust and thorough collection of NPS data. These are described below.

- Use of a semi-structured NPS interview: the Neuropsychiatric Adverse Event Interview [NAEI]) was designed to systematically assess the presence and severity of NPS events of interest through a series of targeted questions. Investigators could record AEs based on the NAEI as they deemed appropriate. The NAEI was developed by Pfizer, in part through discussions with FDA, and was piloted by an external vendor in a study with a subject population similar to EAGLES to ensure subject understanding of the questions.[30] Site personnel were retrained on the tool every 6 months.

- Use of common validated psychiatric rating scales: These included the C-SSRS, the Hospital Anxiety and Depression Scale (HADS), and the Clinical Global Impressions-Improvement scale (CGI-I, focused on psychiatric condition). Investigators could record AEs based on data from these tools as deemed appropriate. Site personnel administering these scales were required to be at least a bachelor's level clinician or nurse. Study personnel were extensively trained on use of these tools and in the case of the C-SSRS, were required to be re-trained every 2 years for the C-SSRS.

- Required MHP evaluations: evaluation by an MHP was required in certain circumstances both during screening and at clinic visits during the treatment and follow-up phases, eg, if the subject answered "yes" on the C-SSRS for item 5 or had a CGI-I score >11 and any subject who had an NPS AE endpoint event. Investigators could also request an MHP evaluation at any time per their discretion. Investigators could record AEs based on these evaluations as deemed appropriate.

- Proxy AE reporting: AEs volunteered by family and physicians of the subject were also recorded in addition to those volunteered by the subject themselves. This process was facilitated by providing subjects with emergency contact information cards that they could share with close contacts, eg, family and physicians, which explained the subject's participation in the study and listed the NPS events of concern to facilitate the proxy reporting of these events to investigative site personnel.

- The description of the event as reported by the subject or proxy for the subject was recorded verbatim as part of the AE collection process. These verbatim descriptions provided an additional dimension to the Investigator's medical interpretation of the events and were noted in prose safety narratives prepared for events of interest. Some examples of subject verbatim text from various treatment arms including placebo are shown below. These examples are for events that met the criteria for the primary NPS AE endpoint.

    - "just suddenly get the feeling of anger and get angry towards people just out of the blue. I've been yelling at people and I never yell. This is not like me at all." (hostility component)

    - Subject's girlfriend stated "My boyfriend hit me in the head with a gun and cracked my skull." (aggression component)

    - "I just got tired of feeling that way (angry and anxious) and thought I should just end it all. I put a loaded gun to my mouth." (suicide behavior component)

    - "Thought about walking into traffic. Feeling lasted 3-4 hours." (suicidal ideation component)

2.1.6. Composite Neuropsychiatric Endpoint

A composite AE endpoint was developed specifically for EAGLES, through discussion with FDA, in consideration of the variable nature of the NPS events reported in postmarketing reports. Use of a composite endpoint allowed for increased sensitivity in detecting treatment and/or cohort differences in the rates of NPS events. This composite endpoint was discussed and agreed upon with FDA and specified in the study protocol and Statistical Analysis Plan (SAP). The NPS AE endpoint was composed of 16 components, representing distinct psychiatric constructs, although some components were closely related. These components were selected to cover the spectrum of events reported in postmarketing cases and reflected in the CHANTIX label. The 16 components were: agitation, aggression, anxiety, delusions, depression, feeling abnormal, hallucinations, homicidal ideation, hostility, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, and suicide. As shown in Table 2, each component was composed of 1 or more Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs); in total there were 261 PTs in the composite endpoint (see Appendix 1 for an explanation of MedDRA coding). To be considered part of the composite endpoint, AEs in the anxiety, depression, feeling abnormal, and hostility components had to be rated 'severe' in intensity (see Section 2.4 for an explanation of severity ratings) by the Investigator while AEs in all other components could be either "moderate" or "severe". The severity criteria were imposed to minimize inclusion of less

clinically significant events, including some typically associated with nicotine withdrawal (eg, anxiety and depression). Events rated as "mild" by the Investigator were not included in the endpoint at all. The restriction of the anxiety, depression, feeling abnormal, and hostility components to" severe" only events was requested by FDA.

Table 2. List of MedDRA Preferred Terms in Each Component of the Primary Composite NPS Adverse Event Endpoint

Components with severe intensity events only

Anxiety: Adjustment disorder with anxiety, Acrophobia, Activation syndrome, Acute stress disorder, Agoraphobia, Animal phobia, Anticipatory anxiety, Anxiety, Anxiety disorder, Anxiety disorder due to a general medical condition, Arachnophobia, Autophobia, Burnout syndrome, Claustrophobia, Compulsions, Dysmorphophobia, Fear, Fear of animals, Fear of closed spaces, Fear of crowded places, Fear of death, Fear of disease, Fear of eating, Fear of falling, Fear of injection, Fear of open spaces, Fear of pregnancy, Fear of weight gain, Generalised anxiety disorder, Haphephobia, Hydrophobia, Impatience, Impulse-control disorder, Impulsive behaviour, Limited symptom panic attack, Nervousness, Neurosis, Noctiphobia, Nocturnal fear, Nosophobia, Obsessive thoughts, Obsessive-compulsive disorder, Ochlophobia, Osmophobia, Paruresis, Performance fear, Phagophobia, Phobia, Phobia of driving, Phobia of exams, Phobia of flying, Phobic avoidance, Phonophobia, Photaugiaphobia, Post-traumatic stress disorder, Pyromania, Social fear, Social phobia, Somatoform disorder cardiovascular, Stress, Tension, Thanatophobia, Trichotillomania.

Depression: Adjustment disorder with depressed mood, Adjustment disorder with mixed anxiety and depressed mood, Agitated depression, Anhedonia, Apathy, Asocial behaviour, Boredom, Crying, Decreased interest, Depressed mood, Depression, Depressive symptom, Dysthymic disorder, Feeling guilty, Feeling of despair, Feelings of worthlessness, Laziness, Major depression, Menopausal depression, Mood disorder due to a general medical condition, Morose, Negative thoughts, Postpartum depression, Psychomotor retardation, Regressive behaviour, Seasonal affective disorder, Self esteem decreased, Social avoidant behaviour, Tearfulness.

Feeling Abnormal: Abnormal behavior, Activities of daily living impaired, Altered state of consciousness, Bedridden, Bradyphrenia, Catatonia, Circumstantiality, Confabulation, Confusional arousal, Confusional state, Consciousness fluctuating, Depersonalisation, Derailment, Derealisation, Disability, Disorientation, Dissociation, Dissociative amnesia, Dissociative disorder, Dissociative fugue, Dissociative identity disorder, Dreamy state, Dyslogia, Emotional disorder, Emotional distress, Feeling abnormal, Feeling drunk, Ideas of reference, Illogical thinking, Impaired driving ability, Impaired reasoning, Impaired self-care, Impaired work ability, Loose associations, Magical thinking, Mental disorder, Mental impairment, Mental status changes, Mood altered, Morbid thoughts, Nervous system disorder, Obsessive rumination, Performance status decreased, Perseveration, Personality change, Poverty of thought content, Pseudodementia, Psychiatric symptom, Tachyphrenia, Tangentiality, Thinking abnormal, Thought blocking, Trance.

Hostility: Antisocial behavior, Belligerence, Hostility, Intermittent explosive disorder, Psychopathic personality.

Components with moderate or severe intensity events

Agitation: Agitation, Disturbance in attention, Hyperkinesia, Restlessness.

Aggression: Aggression, Anger, Antisocial personality disorder, Dysphoria, Homicide, Incest, Physical abuse, Physical assault, Sexual abuse, Spousal abuse, Verbal abuse, Violence-related symptom.

Delusions: Alice in wonderland syndrome, Cotard's syndrome, Deja vu, Delusion, Delusion of grandeur, Delusion of reference, Delusion of replacement, Delusional disorder, erotomanic type, Delusional disorder, grandiose type, Delusional disorder, jealous type, Delusional disorder, mixed type, Delusional disorder, persecutory type, Delusional disorder, somatic type, Delusional disorder, unspecified type, Delusional perception, Delusions, mixed, Depressive delusion, Erotomanic delusion, Grandiosity, Jamais vu, Jealous delusion, Persecutory delusion, Somatic delusion, Thought broadcasting, Thought insertion, Thought withdrawal.

Hallucination: Hallucination, Hallucination, auditory, Hallucination, gustatory, Hallucination, olfactory, Hallucination, synaesthetic, Hallucination, tactile, Hallucination, visual, Hallucinations, mixed, Hypnagogic hallucination, Hypnopompic hallucination, Illusion, Somatic hallucination.

Mania: Affect lability, Bipolar disorder, Bipolar I disorder, Bipolar II disorder, Cyclothymic disorder, Disinhibition, Elevated mood, Euphoric mood, Flight of ideas, Hypomania, Mania, Mood swings, Self esteem inflated.

Panic: Breath holding, Panic attack, Panic disorder, Panic disorder with agoraphobia, Panic disorder without agoraphobia, Panic reaction.

Paranoia: Hypervigilance, Paranoia, Paranoid personality disorder, Suspiciousness.

Table 2. List of MedDRA Preferred Terms in Each Component of the Primary Composite NPS Adverse Event Endpoint

Psychosis: Acute psychosis, Brief psychotic disorder with marked stressors, Brief psychotic disorder without marked stressors, Flat affect, Hysterical psychosis, Inappropriate affect, Negativism, Psychotic behaviour, Psychotic disorder, Psychotic disorder due to a general medical condition, Reactive psychosis, Schizoaffective disorder, Schizoaffective disorder bipolar type, Schizoaffective disorder depressive type, Schizophrenia, Schizophrenia simple, Schizophrenia, catatonic type, Schizophrenia, disorganised type, Schizophrenia, paranoid type, Schizophrenia, residual type, Schizophrenia, undifferentiated type, Schizophreniform disorder, Schizotypal personality disorder, Shared psychotic disorder, Transient psychosis.

Homicidal Ideation: Homicidal ideation

Suicidal Behavior: Intentional self-injury, Self injurious behaviour, Suicidal behaviour, Suicide attempt.

Suicidal Ideation: Self-injurious ideation, Suicidal ideation.

Suicide: Completed suicide, Depression suicidal.
MedDRA=Medical Dictionary for Regulatory Activities.
MedDRA Version 18.0

2.1.7. Study Limitations

Although EAGLES was robustly designed study to evaluate the NPS safety profile of varenicline (and bupropion), as with most clinical trials, some inherent limitations may affect interpretation of the results, including:

- inclusion was restricted to moderate to heavy smokers, those smoking 10 or greater cigarettes per day (limitation primarily for efficacy).
- only smokers with psychiatric disorders who were stable (with or without treatment) or who had previous psychiatric conditions that were in remission were allowed to enroll.
- the scope of the primary diagnoses allowed for inclusion was restricted to 4 major disease categories (mood disorders, anxiety disorders, psychosis, and borderline personality disorders) and excluded people with current substance abuse disorders or at imminent risk for suicide.
- the 24 week duration of the study and the frequent study visits might not mirror the real world experience of the majority of smokers attempting to quit, for whom such a strong support system might not be available.

Restrictions on the psychiatric population were implemented to ensure a subject's suitability, in terms of personal safety, for initiating a smoking cessation attempt and their ability to follow study procedures, factors which would have counterparts in a real world setting as well. Additionally, although subjects could not have a primary diagnosis of substance abuse, they could have had a co-morbid diagnosis of substance abuse.

An additional limitation was that although the study was adequately sized to estimate the rates of the composite endpoint, there was limited precision to detect rare NPS AEs.

2.2. Study Conduct

2.2.1. Study Oversight

EAGLES was conducted in accordance with standard Pfizer study procedures and study oversight was in accordance with Pfizer's quality management system. The quality management system entails a combination of scheduled on-site monitoring, compliance oversight visits to the study sites, and Investigator site audits. Potential significant quality issues identified as a result of monitoring/oversight were escalated and evaluated to determine appropriate further action.

A total of 4451 on-site monitoring visits were conducted during the course of the study across all 142 sites that screened subjects. A total of 404 compliance oversight visits were completed at 140 sites during the conduct of the study. A total of 26 investigator site audits were conducted over the study period.

2.2.1.1. Protocol Deviations

Study oversight procedures identified protocol violations which were then discussed with site personnel. The major protocol violations are summarized in Table 3 for the study overall and by treatment group.

Table 3. Summary of Major Protocol Deviations in EAGLES by Issue Category and Treatment Group

	Number (%) of Subjects				
Issue Category	Varenicline (N=2016)	Bupropion (N=2006)	NRT (N=2022)	Placebo (N=2014)	Total (N=8058)
AE/SAE reporting	3 (0.15)	3 (0.15)	3 (0.15)	2 (0.10)	11 (0.14)
Disallowed Medications	60 (2.98)	47 (2.34)	52 (2.57)	58 (2.88)	217 (2.69)
Inclusion/Exclusion Criteria	84 (4.17)	96 (4.79)	87 (4.30)	85 (4.22)	352 (4.37)
Informed Consent	1 (0.05)	2 (0.10)	2 (0.10)	2 (0.10)	7 (0.09)
IP Administration/Study Treatment	7 (0.35)	12 (0.60)	16 (0.79)	16 (0.79)	51 (0.63)
Procedures/Tests	25 (1.24)	35 (1.74)	32 (1.58)	34 (1.69)	126 (1.56)
Visit Schedule	0	0	0	0	0
Withdrawal Criteria	0	0	0	0	0
Other	9 (0.45)	18 (0.90)	6 (0.30)	16 (0.79)	49 (0.61)

AE=adverse event; IP=investigational product; N=number of subjects per treatment arm; PD=protocol deviation; SAE=serious adverse event.
Subjects were counted only once per issue category and major PD designation.
Includes all subjects who received at least 1 partial dose of study treatment.
Percentages were calculated in reference to N.

Of note, study monitoring identified 49 subjects who were initially randomized to the incorrect cohort. For 44 of these subjects, data were corrected prior to database lock and release, and subjects were analyzed in the correct non-PHx and PHx cohorts. For 4 of the 5 remaining subjects (1 bupropion, 2 NRT, 1 placebo), the initial randomization (non-PHx cohort) was correct, based on information available at that time; however, later in the course of the study, new information became available that would have changed the subject's cohort assignment (PHx), had it been disclosed at screening. The final subject, treated with

bupropion, was randomized to the PHx cohort due to incorrect completion of the SCID. The SCID should have been negative, and the subject should have been in the non-PHx cohort.

For these 5 subjects who were not classified correctly for study analyses, 1 had AEs that met the severity criteria for the NPS AE endpoint. This placebo subject, who was in the non-PHx cohort, had moderate panic reaction and moderate schizophrenia; however, these events were post-treatment emergent (more than 30 days after the last dose of study treatment). As a result, they were not included in the primary NPS AE endpoint.

Oversight activities also raised data quality issues for 2 study sites. To determine if these data quality issues had an impact on the study results, sensitivity analyses were conducted, which removed from the primary endpoint analysis these sites, both individually and together. These analyses indicated that data from these sites did not significantly impact the study results.

2.3. Study Population

2.3.1. Subject Disposition

Overall, 8144 subjects at 140 investigative centers in 16 countries were randomized. Almost half of all sites (65 of 140) and just over half of all subjects (4260 of 8144 subjects) were in the US. Other countries represented included: Argentina, Australia, Brazil, Bulgaria, Canada, Chile, Denmark, Finland, Germany, Mexico, New Zealand, Russian Federation, Slovakia, South Africa, and Spain. The number of subjects in each cohort (~4000) and in each treatment group within a cohort (~1000) was well balanced.

Subject disposition from the point of randomization is summarized in Table 4 for the study overall and by cohort.

Table 4. EAGLES Subject Disposition Overall and by Cohort

	Number (%) of Subjects			
	Varenicline	**Bupropion**	**NRT**	**Placebo**
Overall				
Assigned to Study Treatment	2037	2034	2038	2035
Randomized but Not Treated	21	28	16	21
Randomized and Treated	2016 (100)	2006 (100)	2022 (100)	2014 (100)
Completed treatment	1565 (77.6)	1537 (76.6)	1538 (76.1)	1528 (75.9)
Discontinued treatment	451 (22.4)	469 (23.4)	484 (23.9)	486 (24.1)
Completed Study	1598 (79.3)	1586 (79.1)	1557 (77.0)	1552 (77.1)
OTIS completers	138	152	145	123
Discontinued Study	418 (20.7)	420 (20.9)	465 (23.0)	462 (22.9)
During treatment phase[a]	293 (70.1)	281 (66.9)	303 (65.2)	335 (72.5)
Post-treatment phase[a]	125 (29.9)	139 (33.1)	162 (34.8)	127 (27.5)
Non-Psychiatric History				
Assigned to Study Treatment	1005	1001	1013	1009
Randomized but Not Treated	15	12	7	10
Randomized and Treated	990 (100)	989 (100)	1006 (100)	999 (100)
Completed treatment	793 (80.1)	772 (78.1)	777 (77.2)	803 (80.4)
Discontinued treatment	197 (19.9)	217 (21.9)	229 (22.8)	196 (19.6)
Completed Study	787 (79.5)	783 (79.2)	767 (76.2)	787 (78.8)

Table 4. EAGLES Subject Disposition Overall and by Cohort

	Number (%) of Subjects			
	Varenicline	**Bupropion**	**NRT**	**Placebo**
OTIS completers	52	68	61	35
Discontinued Study	203 (20.5)	206 (20.8)	239 (23.8)	212 (21.2)
During treatment phase[a]	139 (68.5)	130 (63.1)	157 (65.7)	154 (72.6)
Post-treatment phase[a]	64 (31.5)	76 (36.9)	82 (34.3)	58 (27.4)
Psychiatric History				
Assigned to Study Treatment	1032	1033	1025	1026
Randomized but Not Treated	6	16	9	11
Randomized and Treated	1026 (100)	1017 (100)	1016 (100)	1015 (100)
Completed treatment	772 (75.2)	765 (75.2)	761 (74.9)	725 (71.4)
Discontinued treatment	254 (24.8)	252 (24.8)	255 (25.1)	290 (28.6)
Completed Study	811 (79.0)	803 (79.0)	790 (77.8)	765 (75.4)
OTIS completers	86	84	84	88
Discontinued Study	215 (21.0)	214 (21.0)	226 (22.2)	250 (24.6)
During treatment phase[a]	154 (71.6)	151 (70.6)	146 (64.6)	181 (72.4)
Post-treatment phase[a]	61 (28.4)	63 (29.4)	80 (35.4)	69 (27.6)

a. Percentages are based on the number of subjects who discontinued the study.
NRT=nicotine replacement therapy; OTIS=Off Treatment and In Study.
Includes all subjects who received at least 1 partial dose of study drug.

Overall, approximately 78% of subjects in each treatment group completed the study and a slightly lower percentage completed treatment. Treatment completion rates were similar in the PHx cohort compared to the non-PHx cohort in all treatment groups. Both study and treatment completion rates for varenicline subjects were at the high end of the range seen across treatments. Most subjects who discontinued the study did so during the treatment phase (~70%).

Reasons for discontinuation from treatment are shown in Table 5 for the non-PHx cohort and Table 6 for the PHx cohort.

Table 5. Reasons for Discontinuation from Treatment — Non-Psychiatric History Cohort

	Number (%) of Subjects			
	Varenicline N=990	**Bupropion N=989**	**NRT N=1006**	**Placebo N=999**
Discontinued treatment	197 (19.9)	217 (21.9)	229 (22.8)	196 (19.6)
Adverse event	57 (5.8)	74 (7.5)	73 (7.3)	26 (2.6)
Insufficient clinical response	6 (0.6)	3 (0.3)	9 (0.9)	7 (0.7)
Lost to follow-up	42 (4.2)	39 (3.9)	37 (3.7)	38 (3.8)
Medication error without associated adverse event	0	1 (0.1)	0	0
No longer meets eligibility criteria	0	3 (0.3)	0	2 (0.2)
No longer willing to participate in study	61 (6.2)	63 (6.4)	79 (7.9)	89 (8.9)
Other	29 (2.9)	29 (2.9)	26 (2.6)	26 (2.6)
Protocol violation	1 (0.1)	3 (0.3)	4 (0.4)	5 (0.5)
Withdrawn due to pregnancy	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.2)

Table 5. Reasons for Discontinuation from Treatment — Non-Psychiatric History Cohort

	Number (%) of Subjects			
	Varenicline	**Bupropion**	**NRT**	**Placebo**
Subject died	0	1 (0.1)	0	1 (0.1)

NRT=nicotine replacement therapy; N=total number of subjects per treatment group.
Includes all subjects who received at least 1 partial dose of study treatment.

In the non-PHx cohort, across all treatment groups, reason for discontinuation from treatment was most frequently categorized as 'adverse event', 'lost to follow-up', 'no longer willing to participate', and 'other'. The percentages of subjects in each of the categories 'lost to follow-up', 'no longer willing to participate', and 'other' were generally similar across treatment groups, while fewer placebo subjects than subjects in the active treatment groups were categorized as discontinuing treatment due to the category 'adverse event'.

Table 6. Reasons for Discontinuation from Treatment — Psychiatric History Cohort

	Number (%) of Subjects			
	Varenicline N=1026	**Bupropion N=1017**	**NRT N=1016**	**Placebo N=1015**
Discontinued treatment	254 (24.8)	252 (24.8)	255 (25.1)	290 (28.6)
Adverse event	108 (10.5)	101 (9.9)	85 (8.4)	94 (9.3)
Insufficient clinical response	4 (0.4)	4 (0.4)	8 (0.8)	10 (1.0)
Lost to follow-up	44 (4.3)	37 (3.6)	36 (3.5)	44 (4.3)
Medication error without associated adverse event	1 (0.1)	0	0	1 (0.1)
No longer meets eligibility criteria	1 (0.1)	6 (0.6)	4 (0.4)	3 (0.3)
No longer willing to participate in study	62 (6.0)	70 (6.9)	66 (6.5)	83 (8.2)
Other	30 (2.9)	30 (2.9)	49 (4.8)	49 (4.8)
Protocol violation	4 (0.4)	1 (0.1)	6 (0.6)	4 (0.4)
Withdrawn due to pregnancy	0	2 (0.2)	1 (0.1)	1 (0.1)
Subject died	0	1 (0.1)	0	1 (0.1)

NRT=nicotine replacement therapy; N=total number of subjects per treatment group.
Includes all subjects who receive at least 1 partial dose of study treatment.

In the PHx cohort, reasons for discontinuing treatment were similar to those in the non-PHx cohort across all treatment groups (most frequent reasons categorized as 'adverse event', 'lost to follow-up', 'no longer willing to participate', and 'other'), although a higher percentage of subjects in the PHx cohort discontinued treatment due to an AE than in the non-PHx cohort (8.4% - 10.5% versus [vs] 2.6% - 7.5%, respectively). In the PHx cohort, the percentages of subjects in each of these categories were generally similar across treatment groups.

A further analysis of subjects whose treatment discontinuation was categorized as 'lost to follow-up', 'no longer willing to participate', and 'other' was performed to evaluate whether any of these subjects may, in fact, have possibly discontinued due to an AE although their discontinuation was not reported as such. For this analysis, the Investigators' comments in

the discontinuation category field were reviewed along with AE information for the subject. Based on the comments, subjects were further categorized as having discontinued for a reason that was clearly not AE-related ('clear non-AE reason', eg, subject moved or changed jobs), a reason which was unclear regarding a relation to an AE ('unclear reason'), or a reason which implied the discontinuation was possibly due to an AE ('possibly due to AE'). The results of this analysis are shown in Table 7.

Table 7. Evaluation of Subjects Reported as Discontinuing Treatment Due to Reasons of 'Lost to Follow-Up', 'No Longer Willing to Participate', and 'Other' – By Cohort

	Non-Psychiatric Cohort			Psychiatric Cohort		
	Lost to follow-up	No longer willing to participate	Other	Lost to follow-up	No longer willing to participate	Other
Varenicline						
Overall	**42**	**61**	**29**	**44**	**62**	**30**
Possibly due to AE	0	3	3	0	5	2
Bupropion						
Overall	**39**	**63**	**29**	**37**	**70**	**30**
Possibly due to AE	0	0	1	0	4	3
NRT						
Overall	**37**	**79**	**26**	**36**	**66**	**49**
Possibly due to AE	0	2	1	1	1	1
Placebo						
Overall	**38**	**89**	**26**	**44**	**83**	**49**
Possibly due to AE	0	0	1	0	4	2

AE=adverse event; NRT=nicotine replacement therapy.
Includes all subject who received at least 1 partial dose of study drug

This retrospective analysis suggests that there were relatively few subjects who potentially discontinued treatment due to an AE of any type.

2.3.2. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics are shown in Table 8 (non-PHx cohort) and Table 9 (PHx cohort).

Table 8. Demographic and Other Baseline Characteristics – Non-Psychiatric History Cohort

Baseline Characteristics	Varenicline (N=990)	Bupropion (N=989)	NRT (N=1006)	Placebo (N=999)
Age (years)				
n	990	989	1006	999
Mean (SD)	45.8 (13.0)	46.0 (13.0)	46.1 (12.8)	45.9 (12.8)

Table 8. Demographic and Other Baseline Characteristics – Non-Psychiatric History Cohort

Baseline Characteristics	Varenicline (N=990)	Bupropion (N=989)	NRT (N=1006)	Placebo (N=999)
Min, Max	18, 73	18, 75	18, 75	18, 74
Gender, n (%)				
Male	510 (51.5)	504 (51.0)	499 (49.6)	490 (49.0)
Female	480 (48.5)	485 (49.0)	507 (50.4)	509 (51.0)
Race, n (%)				
White	819 (82.7)	820 (82.9)	837 (83.2)	817 (81.8)
Black	135 (13.6)	116 (11.7)	127 (12.6)	126 (12.6)
Asian	14 (1.4)	16 (1.6)	13 (1.3)	19 (1.9)
Other	22 (2.2)	37 (3.7)	29 (2.9)	37 (3.7)
Weight (kg)				
n	980	984	1000	992
Mean (SD)	80.0 (19.5)	80.4 (20.1)	81.6 (19.6)	80.6 (19.3)
Min, Max	39.8, 176.8	40.5, 171.5	38.4, 201.8	42.0, 169.2
Psychiatric Characteristics				
Prior psychiatric medications, n (%)				
Psychoanaleptics	27 (2.7)	27 (2.7)	33 (3.3)	36 (3.6)
Psycholeptics	61 (6.2)	58 (5.9)	68 (6.8)	73 (7.3)
HADS (Total Score)				
n	990	989	1006	999
Mean (SD)	4.35 (4.44)	4.08 (4.09)	4.20 (4.11)	4.50 (4.33)
Min, Max	0, 28	0, 24	0, 25	0, 22
C-SSRS Lifetime[a]				
n (%)	49 (4.9)	44 (4.4)	52 (5.2)	49 (4.9)
Smoking Characteristics				
Total number of years subject smoked				
n	990	989	1006	999
Mean (SD)	27.8 (12.8)	28.2 (13.0)	28.2 (12.8)	28.2 (12.6)
Min, Max	2, 64	2, 60	1, 63	2, 62
Total number of lifetime serious quit attempts[b]				
None, n (%)	181 (18.3)	181 (18.3)	174 (17.3)	204 (20.4)
n	990	989	1006	999
Mean (SD)	3.3 (13.8)	3.4 (10.3)	3.1 (4.2)	3.2 (7.4)
Min, Max	0, 400	0, 300	0, 31	0, 108
Number of subjects with ≥1 previous serious quit attempt, n (%)	809 (81.7)	808 (81.7)	832 (82.7)	795 (79.6)
Previous use of medication for quit attempt (most recent attempt), n (%)				
Varenicline	132 (13.3)	144 (14.6)	152 (15.1)	136 (13.6)
Bupropion	92 (9.3)	91 (9.2)	93 (9.2)	90 (9.0)
NRT	272 (27.5)	307 (31.0)	325 (32.3)	305 (30.5)
Average number of cigarettes per day over the last month prior to study entry				
n	990	989	1005	999
Mean (SD)	20.8 (8.3)	20.6 (7.8)	20.8 (8.2)	20.5 (7.9)
Min, Max	10, 80	6, 60	10, 60	10, 60
FTND (Total Score)				
n	989	987	1006	998
Mean (SD)	5.49 (1.98)	5.50 (2.02)	5.56 (1.95)	5.51 (2.01)
Min, Max	0, 10	0, 10	0, 10	0, 10

a. C-SSRS (positive response for suicidal behavior or/and ideation).
b. Serious quit attempt = more than 24 hours.
C-SSRS=Columbia Suicide Severity Rating Scale; HADS=Hospital Anxiety and Depression Scale, 14

Table 8. Demographic and Other Baseline Characteristics – Non-Psychiatric History Cohort

Baseline Characteristics	Varenicline (N=990)	Bupropion (N=989)	NRT (N=1006)	Placebo (N=999)

individual item responses, ranging in increasing severity from 0 to 3; Max=maximum; Min=minimum; N=number of subjects per treatment arm; n=number of subjects with observation of interest; SD=standard deviation; NRT=nicotine replacement therapy; FTND= Fagerström Test for Nicotine Dependence, scores range from 1 (low dependence) to 10 (high dependence).
Includes all subjects who received at least 1 partial dose of study treatment.

Table 9. Demographic and Other Baseline Characteristics – Psychiatric History Cohort

Baseline Characteristics	Varenicline (N=1026)	Bupropion (N=1017)	NRT (N=1016)	Placebo (N=1015)
Age (years)				
n	1026	1017	1016	1015
Mean (SD)	47.2 (11.8)	46.7 (12.2)	47.6 (11.5)	46.9 (11.5)
Min, Max	18, 74	18, 75	18, 75	18, 75
Gender, n (%)				
Male	392 (38.2)	388 (38.3)	384 (37.8)	386 (38.0)
Female	634 (61.8)	629 (61.7)	632 (62.2)	629 (62.0)
Race, n (%)				
White	849 (82.7)	816 (80.2)	804 (79.1)	822 (81.0)
Black	145 (14.1)	165 (16.2)	176 (17.3)	155 (15.3)
Asian	5 (0.5)	10 (1.0)	11 (1.1)	7 (0.7)
Other	27 (2.6)	26 (2.6)	25 (2.5)	30 (3.0)
Unspecified	0	0	0	1 (0.1)
Psychiatric Characteristics				
Prior psychiatric medications, n (%)				
Psychoanaleptics	423 (41.2)	354 (34.8)	369 (36.3)	380 (37.4)
Psycholeptics	309 (30.1)	298 (29.3)	326 (32.1)	295 (29.1)
HADS (Total Score)				
n	1026	1017	1015	1015
Mean (SD)	8.26 (6.45)	8.74 (6.92)	8.37 (6.58)	8.21 (6.22)
Min, Max	0, 30	0, 36	0, 31	0, 36
C-SSRS Lifetime[b]				
n (%)	353 (34.4)	363 (35.7)	339 (33.4)	358 (35.3)
Primary Diagnosis in SCID of:				
Mood disorders, n (%)	731 (71.2)	716 (70.4)	713 (70.2)	722 (71.1)
Anxiety disorders, n (%)	193 (18.8)	200 (19.7)	195 (19.2)	194 (19.1)
Psychotic disorders, n (%)	95 (9.3)	96 (9.4)	99 (9.7)	96 (9.5)
Personality disorder[a], n (%)	7 (0.7)	5 (0.5)	9 (0.9)	3 (0.3)
Smoking Characteristics				
Total number of years subject smoked				
n	1026	1017	1016	1015
Mean (SD)	28.9 (11.8)	28.2 (12.4)	28.9 (11.9)	28.3 (11.6)
Min, Max	2, 60	2, 56	2, 58	2, 56
Total number of lifetime serious quit attempts[c]				
None, n (%)	171 (16.7)	174 (17.1)	165 (16.2)	161 (15.9)
n	1026	1017	1016	1015
Mean (SD)	3.4 (7.7)	3.5 (6.9)	3.3 (5.3)	3.6 (10.9)

Table 9. Demographic and Other Baseline Characteristics – Psychiatric History Cohort

Baseline Characteristics	Varenicline (N=1026)	Bupropion (N=1017)	NRT (N=1016)	Placebo (N=1015)
Min, Max	0, 200	0, 100	0, 77	0, 300
Number of subjects with ≥1 previous serious quit attempt, n (%)	855 (83.3)	843 (82.9)	851 (83.8)	854 (84.1)
Previous use of medication for quit attempt (most recent attempt), n (%)				
Varenicline	149 (14.5)	194 (19.1)	168 (16.5)	161 (15.9)
Bupropion	102 (9.9)	114 (11.2)	102 (10.0)	101 (10.0)
NRT	373 (36.4)	326 (32.1)	356 (35.0)	338 (33.3)
Average number of cigarettes per day over the last month prior to study entry				
n	1026	1017	1016	1015
Mean (SD)	20.6 (8.0)	20.5 (8.2)	20.8 (9.1)	20.7 (8.2)
Min, Max	5, 70	10, 60	10, 120	10, 70
FTND (Total Score)				
n	1025	1017	1016	1015
Mean (SD)	6.04 (1.93)	6.06 (1.91)	5.96 (1.95)	5.91 (2.02)
Min, Max	0, 10	0, 10	0, 10	0, 10

a. Limited to borderline personality disorder.
b. C-SSRS (positive response for suicidal behavior or/and ideation).
c. Serious quit attempt = more than 24 hours.
C-SSRS=Columbia Suicide Severity Rating Scale; HADS=Hospital Anxiety and Depression Scale, 14 individual item responses, ranging in increasing severity from 0 to 3; Max=maximum; Min=minimum; N=number of subjects per treatment arm; n=number of subjects with observation of interest; SD=standard deviation; NRT=nicotine replacement therapy; FTND=Fagerström Test for Nicotine Dependence, scores range from 1 (low dependence) to 10 (high dependence); SCID=Structured Clinical Interview for DSM-IV.
Includes all subjects who received at least 1 partial dose of study treatment

Demographic characteristics were similar across treatment arms and generally similar between the 2 cohorts. The mean age was approximately 46 years in the non-PHx cohort and 47 years in the PHx cohort. The majority of subjects were white, approximately 83% in the non-PHx cohort and 81% in the PHx cohort. The gender split in the non-PHx cohort across treatment arms was approximately 50% male/50% female, while in the PHx cohort it was approximately 40% male/60% female. Of note, the majority of postmarketing reports are for female patients.

Per protocol, subjects in the non-PHx cohort did not have a SCID-diagnosed psychiatric disorder. In the PHx cohort the percentages of subjects with each category of primary diagnosis were similar across treatment arms: approximately 70% had mood disorders, 20% anxiety disorders, 10% psychotic disorders, and <1% personality disorders. In the non-PHx cohort, approximately 5% of subjects had positive responses at Screening on the C-SSRS for lifetime suicidal behavior and/or ideation, while for the PHx cohort approximately 35% had positive lifetime responses at Screening.

Baseline smoking characteristics were similar in the 2 cohorts and across all treatment arms within each cohort, including: years smoked (~28), average number of cigarettes per day (~21) and number of quit attempts (3). Fagerstrom Test for Nicotine Dependence (FTND)

total scores were slightly higher in the PHx cohort than in the non-PHx cohort (~6.0 vs 5.5, respectively), but for both cohorts represented moderate dependence.

2.4. Safety

In EAGLES, safety was evaluated primarily through the collection of AEs and the administration of psychiatric rating scales. AEs were defined according to the standard criteria of any untoward medical occurrence in a clinical investigation subject administered a product; the event does not necessarily have to have a causal relationship with the treatment or usage. Both volunteered and solicited AEs were collected at each in-clinic visit both in the treatment phase and the non- treatment follow-up phase. These included Weeks 1, 2, 3, 4, 5, 6, 8, 10, 12, 13, 16, 20 and 24 (see Figure 1). In addition, volunteered AEs were collected at any weekly telephone visits conducted between the clinic visits (Weeks 7, 9, 11, 14, 15, 17, 18, 19, 21, 22, and 23). The NAEI, C-SSRS and other psychiatric rating scales were administered during in-clinic visits only. AEs reported during treatment and for up to 30 calendar days after treatment were considered to be treatment-emergent (see Figure 1). AEs reported from 31 days after the last dose of study drug through the end of the study were considered post-treatment-emergent. Only treatment-emergent AEs are discussed in this document.

Investigators were required to rate the severity of each AE as mild, moderate or severe according to the following standard guidelines:

MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

It is important to note that AE severity is distinct from AE seriousness. For example, an AE could be severe yet not be considered a serious adverse event (SAE) and conversely, an AE of mild or moderate severity could be considered an SAE. The standard regulatory criteria[31] for SAEs include:

- events that result in death or are life threatening,
- events that lead to hospitalization (initial or prolonged),
- events that lead to a disability or permanent damage,
- events that require intervention to prevent permanent impairment or damage,
- congenital anomalies or birth defects resulting from exposure in utero,
- other - important medical events.

As noted above (Section 2.1.5) AEs came from several sources: volunteered by the participant or a proxy for the participant (family/physician), observed by the Investigator, answers to questions on the NAEI deemed to be AEs by the Investigator, and/or responses on

scales (C-SSRS, HADS, CGI-I) or MHP evaluations deemed to be AEs by the Investigator. AEs presented in the sections below are from all sources combined. The decision to record a reported or observed event of any type as an AE was up to the judgment of the Investigator.

2.4.1. Evaluation of Safety

2.4.1.1. NPS AE Endpoint

The primary safety endpoint evaluation was the occurrence of at least 1 treatment-emergent event (treatment plus 30 days) meeting the criteria of the composite endpoint as described in Section 2.1.6.

Pre-specified secondary safety endpoint evaluations related to the primary NPS AE endpoint included:

- Occurrence of each of the components of the primary safety endpoint (based on the allowable severity ratings per component).
- Occurrence of at least 1 treatment-emergent NPS AE included in the composite that was graded as "severe", constituting as such, a "severe-only" NPS AE endpoint.
- Occurrence of each of the components of the "severe-only" NPS AE endpoint.

2.4.1.2. Other Neuropsychiatric Assessments

As noted previously, EAGLES incorporated several scales that allowed for further monitoring of the psychiatric status of study subjects. These were administered at each in-clinic visit and included:

- C-SSRS: widely used semi-structured interview to assess the presence and intensity of suicidal ideation and behavior.
  - Totals of positive individual item responses.

- HADS: a commonly used, self-assessment scale to determine the levels of anxiety and depression.
  - 14 individual item responses, ranging in increasing severity from 0 to 3.
  - Anxiety subscale score (sum of the 7 odd-numbered item response scores; ranges: 0-7 = normal, 8-10 = suggestive, 11-21 = probable).
  - Depression subscale score (sum of the 7 even-numbered item response scores; ranges: 0-7 = normal, 8-10 = suggestive, 11-21 = probable).
  - Overall score (sum of 14 individual item response scores; range 0-42).

- CGI-I: a clinician rated instrument that measures change in subject's psychiatric condition.
  - A single item response (a 7-point rating, with 4 being no change, 1 to 3 being levels of improvement, and 5 to 7 being levels of worsening). Investigators were instructed to rate the subject in regards to their psychiatric status and symptoms.

2.4.1.3. Non-NPS Adverse Events

In addition to NPS AEs in the composite endpoint, all other AEs were also evaluated.

2.4.1.4. Statistical Methods

As noted in Section 2.1.6, the primary safety endpoint was a composite endpoint developed specifically for EAGLES that included 16 components based on 261 MedDRA PTs. The study was designed as an estimation study with a pre-specified precision due to its novel composite endpoint and lack of clinical guidelines for establishing a non-inferiority margin.

The primary and secondary analyses based on the NPS AE endpoint were performed using a generalized linear regression analysis in the safety analysis population (all subjects who received at least 1 dose or partial dose of study medication). The statistical model included treatment arm, cohort, and region, plus the 2-way and 3-way interactions (as specified in the SAP), including possible model reduction by removal of non-significant interaction terms. Risk differences (RDs) and associated 95% confidence intervals (CIs) were estimated for varenicline-placebo and bupropion-placebo comparisons as the primary analyses of the primary study endpoints. Similar calculations for NRT-placebo, varenicline-bupropion, varenicline-NRT, and bupropion-NRT constituted secondary analyses.

For analyses where the model was not specified or could not be performed (due to small sample size) descriptive statistics are provided.

2.4.1.5. Sample Size Determination

The study was sized to attain an adequate level of precision in the estimation of the treatment difference for varenicline and bupropion versus placebo in the incidence of the primary NPS endpoint within each cohort.

For the subjects in the non-PHx cohort, considering both the available data from the varenicline randomized, double-blind, placebo-controlled clinical studies as well as the planned usage of the NAEI to aid in data collection, the incidence estimate for placebo was assumed to be approximately 3.5% for volunteered and solicited NPS AEs included in the primary safety endpoint. If there was an attributable RD of 2.63% (which translated to a 75% increase in the relative risk scale), a sample size of 1000 subjects per treatment arm would provide sufficient precision with an expected 95% CI of 0.75% to 4.50%, ie, a margin of error of ±1.87%.

For the subjects in the PHx cohort, there was no sufficient data available and a 7.0% incidence for the placebo group was assumed. If there was a similar relative risk increase (an attributable RD of 5.25%) the sample size of 1000 subjects per treatment arm would provide sufficient precision with an expected 95% CI of 2.68% to 7.82%, ie, a margin of error of ±2.57%.

The preceding assumptions, when taken together to produce a stratified pooled estimate of RD, suggested that a sample size of 2000 subjects per treatment arm would provide sufficient precision with an expected 95% CI of 2.34% to 5.52%, ie, a margin of error of ±1.59%.

The Independent Data Monitoring Committee (IDMC), which was established to monitor subject safety and who met approximately every 4 months, was also tasked with monitoring the rate of the NPS AE endpoint to ensure the sample size was adequate. Two interim

analyses were planned. A blinded interim analysis was performed after 50% of the subjects had completed at least 20 weeks of the study and an unblinded interim analysis was conducted after 75% of the subjects had completed the study. The IDMC did not notify Pfizer of any concerns about the rate of NPS events and therefore the sample size remained as originally estimated.

2.4.2. Safety Results

The model used for the primary endpoint included treatment, cohort and region (US, non-US). The interaction of treatment by region, cohort by region, and treatment by cohort by region were not significant and were removed from the model (p-values of 0.5870, 0.9294, and 0.2956, respectively).

There was a significant interaction between treatment and cohort at the pre-specified 10% level (p=0.0652), indicating that the RD among treatment pairs was dependent on the cohort. To avoid potential effect masking, results for the 2 cohorts are presented separately, as well for the study overall.

2.4.2.1. Primary NPS AE Endpoint

Table 10 shows the observed rates of the primary NPS AE endpoint overall and by cohort.

Table 10. Observed Rate for the Primary NPS AE Endpoint, Overall and by Cohort

Cohort	Varenicline n/N (%)	Bupropion n/N (%)	NRT n/N (%)	Placebo n/N (%)
Overall	80/2016 (4.0)	90/2006 (4.5)	79/2022 (3.9)	74/2014 (3.7)
Non-Psychiatric History	13/990 (1.3)	22/989 (2.2)	25/1006 (2.5)	24/999 (2.4)
Psychiatric History	67/1026 (6.5)	68/1017 (6.7)	54/1016 (5.3)	50/1015 (4.9)

N=number of subjects per treatment arm; n=number of subjects with an NPS endpoint AE; NPS AE=neuropsychiatric adverse event; NRT=nicotine replacement therapy.
Includes treatment emergent all causality events
Includes all subjects who received at least 1 partial dose of study treatment.

The results of the primary NPS AE endpoint analysis showed low rates overall, which were similar across treatment groups: varenicline 4.0%, bupropion 4.5%, NRT 3.9% and placebo 3.7%. In the non-psychiatric cohort, the observed rates of the composite primary NPS AE endpoint were: 1.3% in the varenicline treatment group, 2.2% in bupropion, 2.5% in NRT, and 2.4% in placebo. Not unexpectedly, the rates of the NPS AE endpoint were higher in the psychiatric cohort compared to the non-psychiatric cohort, but were similar across all treatment groups: 6.5% in varenicline, 6.7% in bupropion, 5.3% in NRT, and 4.9% in placebo.

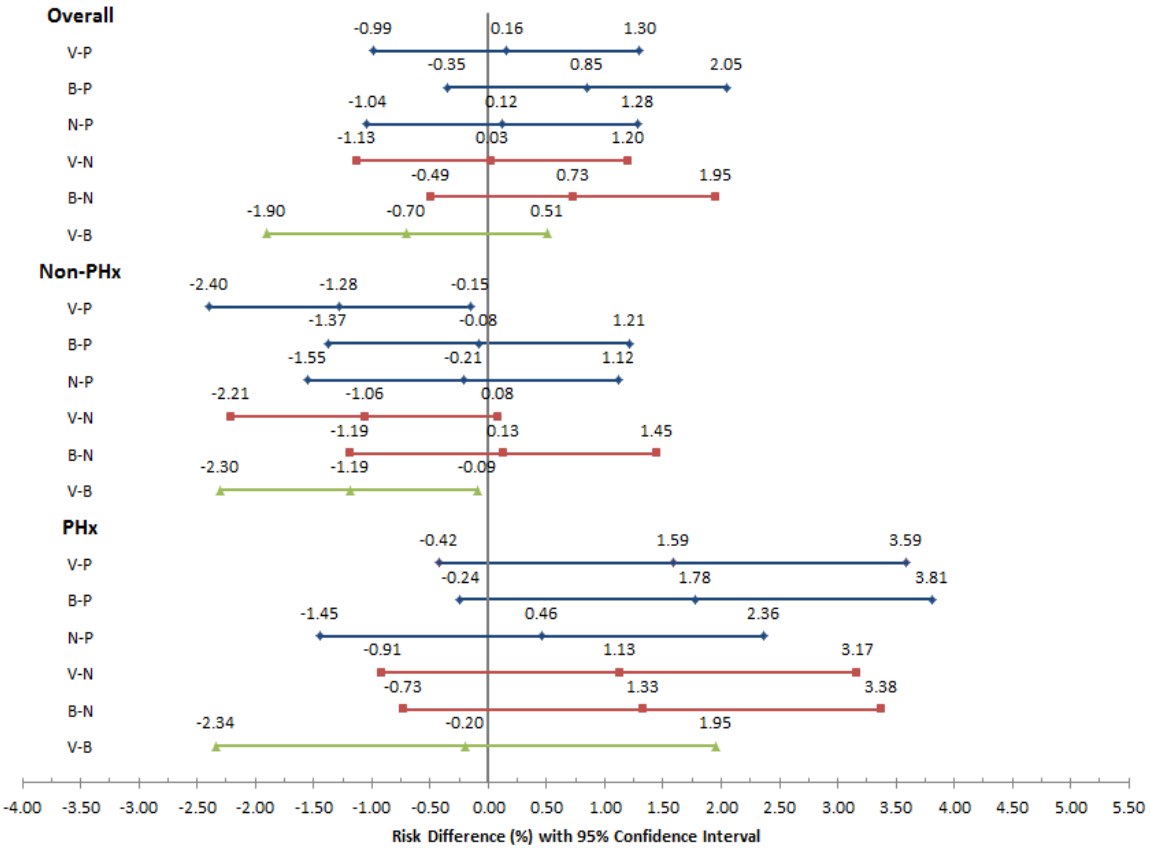
Table 11 provides the model estimated rate of the primary NPS AE endpoint and the RDs for the primary comparisons of varenicline to placebo and bupropion to placebo and all secondary pairwise comparisons, by cohort. Figure 2 provides a graphical representation of the same RD data.

Table 11. Estimation of the Primary NPS AE Endpoint, Overall and by Cohort and Risk Differences for All Treatment Comparisons

	Overall (N=8058)	Non-Psychiatric History (N=3984)	Psychiatric History (N=4074)
Treatment Arm	**Estimated[a] NPS AE (% [95% CI])**		
Varenicline	3.83 (3.02, 4.65)	1.25 (0.60, 1.90)	6.42 (4.91, 7.93)
Bupropion	4.53 (3.63, 5.42)	2.44 (1.52, 3.36)	6.62 (5.09, 8.15)
NRT	3.80 (2.97, 4.63)	2.31 (1.37, 3.25)	5.29 (3.92, 6.66)
Placebo	3.68 (2.87, 4.49)	2.53 (1.59, 3.47)	4.83 (3.51, 6.15)
Treatment Comparisons	**Risk Difference[b] in NPS AE (% [95% CI])**		
Primary Comparisons			
Varenicline vs Placebo	0.16 (-0.99, 1.30)	-1.28 (-2.40, -0.15)	1.59 (-0.42, 3.59)
Bupropion vs Placebo	0.85 (-0.35, 2.05)	-0.08 (-1.37, 1.21)	1.78 (-0.24, 3.81)
Secondary Comparisons			
NRT vs Placebo	0.12 (-1.04, 1.28)	-0.21 (-1.55, 1.12)	0.46 (-1.45, 2.36)
Varenicline vs Bupropion	-0.70 (-1.90, 0.51)	-1.19 (-2.30, -0.09)	-0.20 (-2.34, 1.95)
Varenicline vs NRT	0.03 (-1.13, 1.20)	-1.06 (-2.21, 0.08)	1.13 (-0.91, 3.17)
Bupropion vs NRT	0.73, (-0.49, 1.95)	0.13 (-1.19, 1.45)	1.33 (-0.73, 3.38)

a. Based on least-squares means analysis, point estimate, and its 95% CI.
b. Risk difference was based on a generalized linear model with terms for treatment, cohort, region, and treatment by cohort interaction. Region used 2-level classification (United States, non-United States).
CI=confidence interval; N=number of subjects per treatment arm; NPS AE=neuropsychiatric adverse event; NRT=nicotine replacement therapy.
Includes all subjects who received at least 1 partial dose of study treatment.

Figure 2. Risk Difference (95% CI) in the Primary NPS AE Endpoint, Overall and by Cohort



B=bupropion; CI=confidence interval; N=nicotine replacement therapy; NPS AE=neuropsychiatric adverse event; P=placebo; V=varenicline.

In the study overall, the primary comparison of varenicline vs placebo had an RD close to zero and a 95% CIs including zero, showing no statistically significant increased risk of NPS AEs in the composite endpoint with varenicline treatment (0.16 [-0.99, 1.30]). Similarly, the secondary pairwise comparisons including varenicline (varenicline vs NRT and varenicline vs bupropion) also showed no statistically significant increased risk of NPS events, with 95% CIs including zero. The primary comparison of bupropion vs placebo had an RD greater than zero and a 95% CI including zero, showing no statistically significant increased risk of NPS AEs in the composite endpoint with bupropion treatment (0.85 [-0.35, 2.05]).

In the non-PHx cohort the RD and 95% CI for the primary comparison of varenicline vs placebo were below zero, showing no increased risk of NPS AEs in the composite endpoint with varenicline treatment (-1.28 [-2.40, -0.15]). Similarly, the secondary pairwise comparisons including varenicline (varenicline vs NRT and varenicline vs bupropion) showed no increased risk of NPS events with varenicline, with RDs below zero and 95% CIs below or including zero. The primary comparison of bupropion vs placebo had an RD close

to zero and a 95% CI including zero, showing no statistically significant increased risk of NPS AEs in the composite endpoint with bupropion treatment (-0.08 [-1.37, 1.21]).

In the PHx cohort the primary comparison of varenicline vs placebo had an RD above zero but a 95% CI including zero, showing no statistically significant increased risk of NPS AEs in the composite endpoint with varenicline treatment (1.59 [-0.42, 3.59]) . Similarly, the secondary pairwise comparisons including varenicline (varenicline vs NRT and varenicline vs bupropion) also showed no statistically significant increased risk of NPS events, with 95% CIs including zero. The primary comparison of bupropion vs placebo had an RD greater than zero and a 95% CI including zero, showing no statistically significant increased risk of NPS AEs in the composite endpoint with bupropion treatment (1.78 [-0.24, 3.81]). The small numerical differences between the treatment groups were evaluated further in pre-specified secondary analyses and in additional exploratory analyses and reviews of subject level data.

Secondary analyses provide additional characterization of the NPS AE endpoint. Figure 3 shows the number of subjects reporting NPS endpoint events in each of the individual components and Table 12 (non-PHx cohort) and Table 13 (PHx cohort) provide details regarding the specific PTs (shown not bolded in the table) within each components (shown bolded in the table) of the NPS AE endpoint.

Figure 3. Number of Subjects Reporting NPS Endpoint Events by Component, Non-Psychiatric Cohort

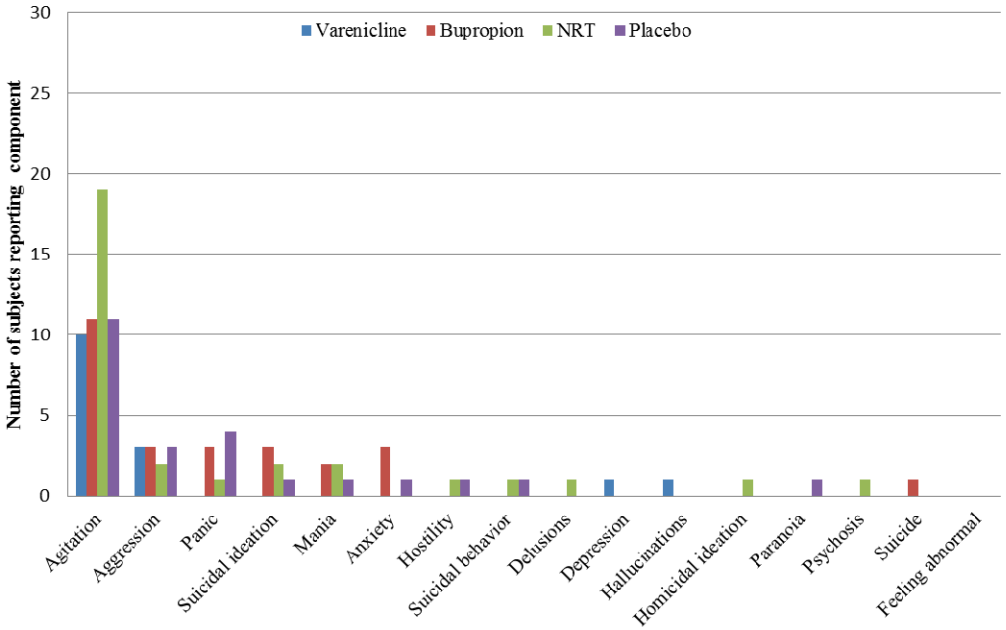


Figure 4. Number of Subjects Reporting NPS Endpoint Events by Component, Psychiatric Cohort

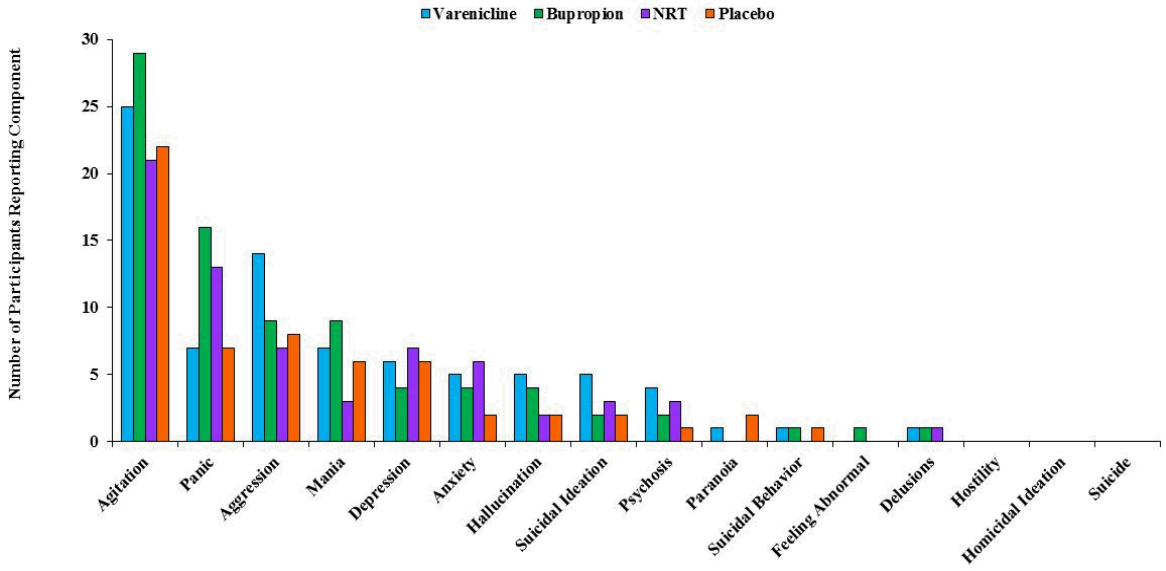


Table 12. Components of the Primary NPS AE Endpoint, Including Preferred Terms, Non-Psychiatric History Cohort

Component Preferred Term	Number (%) of Subjects Varenicline (N=990)	 Bupropion (N=989)	 NRT (N=1006)	 Placebo (N=999)
NPS Endpoint Overall	**13 (1.3)**	**22 (2.2)**	**25 (2.5)**	**24 (2.4)**
Anxiety[a]	**0**	**1 (0.1)**	**0**	**3 (0.3)**
Anxiety	0	1 (0.1)	0	3 (0.3)
Depression[a]	**1 (0.1)**	**0**	**0**	**0**
Depression	1 (0.1)	0	0	0
Feeling Abnormal[a]	**0**	**0**	**0**	**0**
Hostility[a]	**0**	**1 (0.1)**	**1 (0.1)**	**0**
Hostility	0	1 (0.1)	1 (0.1)	0
Agitation[b]	**10 (1.0)**	**11 (1.1)**	**19 (1.9)**	**11 (1.1)**
Agitation	9 (0.9)	6 (0.6)	14 (1.4)	6 (0.6)
Disturbance in attention	2 (0.2)	2 (0.2)	2 (0.2)	2 (0.2)
Restlessness	1 (0.1)	5 (0.5)	3 (0.3)	3 (0.3)
Aggression[b]	**3 (0.3)**	**3 (0.3)**	**2 (0.2)**	**3 (0.3)**
Aggression	1 (0.1)	1 (0.1)	2 (0.2)	1 (0.1)
Anger	1 (0.1)	1 (0.1)	0	1 (0.1)
Dysphoria	1 (0.1)	1 (0.1)	0	1 (0.1)
Delusions[b]	**0**	**0**	**1 (0.1)**	**0**
Somatic delusion	0	0	1 (0.1)	0
Hallucination[b]	**1 (0.1)**	**0**	**0**	**0**

Table 12. Components of the Primary NPS AE Endpoint, Including Preferred Terms, Non-Psychiatric History Cohort

Component Preferred Term	Number (%) of Subjects			
	Varenicline (N=990)	Bupropion (N=989)	NRT (N=1006)	Placebo (N=999)
Hallucination, visual	1 (0.1)	0	0	0
Mania[b]	**0**	**1 (0.1)**	**2 (0.2)**	**2 (0.2)**
Affect lability	0	1 (0.1)	1 (0.1)	1 (0.1)
Bipolar I disorder	0	0	0	1 (0.1)
Elevated mood	0	0	1 (0.1)	0
Panic[b]	**0**	**4 (0.4)**	**1 (0.1)**	**3 (0.3)**
Panic attack	0	4 (0.4)	1 (0.1)	3 (0.3)
Paranoia[b]	**0**	**1 (0.1)**	**0**	**0**
Paranoia	0	1 (0.1)	0	0
Psychosis[b]	**0**	**0**	**1 (0.1)**	**0**
Flat affect	0	0	1 (0.1)	0
Homicidal Ideation[b]	**0**	**0**	**1 (0.1)**	**0**
Homicidal ideation	0	0	1 (0.1)	0
Suicidal Behavior[b]	**0**	**1 (0.1)**	**1 (0.1)**	**0**
Suicide attempt	0	1 (0.1)	1 (0.1)	0
Suicidal Ideation[b]	**0**	**1 (0.1)**	**2 (0.2)**	**3 (0.3)**
Suicidal ideation	0	1 (0.1)	2 (0.2)	3 (0.3)
Suicide[b]	**0**	**0**	**0**	**1 (0.1)**
Completed suicide	0	0	0	1 (0.1)

a. AE severity=Severe only.
b. AE severity=Moderate and severe only.
MedDRA=Medical Dictionary for Regulatory Activities; NPS AE=neuropsychiatric adverse event; N=number of subjects per treatment arm; NRT=nicotine replacement therapy.
Subjects were counted only once per treatment in each row but could be counted in multiple rows.
Includes all subjects who received at least 1 partial dose of study treatment.
MedDRA (v18.0)

Table 13. Components of the Primary NPS AE Endpoint, Including Preferred Terms, Psychiatric History Cohort

Component Preferred Term	Number (%) of Subjects			
	Varenicline (N=1026)	Bupropion (N=1017)	NRT (N=1016)	Placebo (N=1015)
NPS Endpoint Overall	**67 (6.5)**	**68 (6.7)**	**54 (5.3)**	**50 (4.9)**
Anxiety[a]	**5 (0.5)**	**4 (0.4)**	**6 (0.6)**	**2 (0.2)**
Anxiety	4 (0.4)	3 (0.3)	5 (0.5)	2 (0.2)
Anxiety disorder	1 (0.1)	0	0	0
Generalized anxiety disorder	0	1 (0.1)	0	0
Nervousness	0	0	1 (0.1)	0
Tension	1 (0.1)	0	0	0
Depression[a]	**6 (0.6)**	**4 (0.4)**	**7 (0.7)**	**6 (0.6)**
Adjustment disorder with mixed anxiety and depressed mood	0	0	0	1 (0.1)
Crying	0	1 (0.1)	0	0
Decreased interest	0	0	2 (0.2)	0
Depressed mood	0	2 (0.2)	1 (0.1)	1 (0.1)

Table 13. Components of the Primary NPS AE Endpoint, Including Preferred Terms, Psychiatric History Cohort

Component Preferred Term	Number (%) of Subjects Varenicline (N=1026)	 Bupropion (N=1017)	 NRT (N=1016)	 Placebo (N=1015)
Depression	6 (0.6)	0	5 (0.5)	4 (0.4)
Major depression	0	1 (0.1)	0	0
Feeling Abnormal[a]	**0**	**1 (0.1)**	**0**	**0**
Emotional disorder	0	1 (0.1)	0	0
Mental disorder	0	1 (0.1)	0	0
Hostility[a]	**0**	**0**	**0**	**0**
Agitation[b]	**25 (2.4)**	**29 (2.9)**	**21 (2.1)**	**22 (2.2)**
Agitation	16 (1.6)	22 (2.2)	16 (1.6)	14 (1.4)
Disturbance in attention	7 (0.7)	6 (0.6)	3 (0.3)	5 (0.5)
Restlessness	4 (0.4)	2 (0.2)	3 (0.3)	3 (0.3)
Aggression[b]	**14 (1.4)**	**9 (0.9)**	**7 (0.7)**	**8 (0.8)**
Aggression	4 (0.4)	5 (0.5)	3 (0.3)	4 (0.4)
Anger	8 (0.8)	2 (0.2)	3 (0.3)	4 (0.4)
Dysphoria	2 (0.2)	2 (0.2)	1 (0.1)	0
Delusions[b]	**1 (0.1)**	**1 (0.1)**	**1 (0.1)**	**0**
Delusion	1 (0.1)	0	1 (0.1)	0
Thought withdrawal	0	1 (0.1)	0	0
Hallucination[b]	**5 (0.5)**	**4 (0.4)**	**2 (0.2)**	**2 (0.2)**
Hallucination	2 (0.2)	1 (0.1)	0	0
Hallucination, auditory	2 (0.2)	2 (0.2)	1 (0.1)	1 (0.1)
Hallucination, olfactory	0	0	0	1 (0.1)
Hallucination, tactile	0	1 (0.1)	0	0
Hallucination, visual	0	0	1 (0.1)	0
Hypnopompic hallucination	1 (0.1)	0	0	0
Mania[b]	**7 (0.7)**	**9 (0.9)**	**3 (0.3)**	**6 (0.6)**
Affect lability	1 (0.1)	2 (0.2)	2 (0.2)	0
Bipolar I disorder	3 (0.3)	2 (0.2)	0	0
Bipolar II disorder	0	1 (0.1)	0	1 (0.1)
Bipolar disorder	1 (0.1)	0	0	1 (0.1)
Euphoric mood	0	2 (0.2)	0	0
Hypomania	1 (0.1)	1 (0.1)	0	1 (0.1)
Mania	0	2 (0.2)	0	2 (0.2)
Mood swings	1 (0.1)	0	1 (0.1)	1 (0.1)
Panic[b]	**7 (0.7)**	**16 (1.6)**	**13 (1.3)**	**7 (0.7)**
Panic attack	5 (0.5)	11 (1.1)	10 (1.0)	6 (0.6)
Panic disorder	1 (0.1)	3 (0.3)	2 (0.2)	0
Panic disorder with agoraphobia	0	1 (0.1)	0	0
Panic reaction	1 (0.1)	1 (0.1)	2 (0.2)	1 (0.1)
Paranoia[b]	**1 (0.1)**	**0**	**0**	**2 (0.2)**
Paranoia	1 (0.1)	0	0	2 (0.2)
Psychosis[b]	**4 (0.4)**	**2 (0.2)**	**3 (0.3)**	**1 (0.1)**
Acute psychosis	0	1 (0.1)	0	0
Flat affect	2 (0.2)	0	1 (0.1)	0
Inappropriate affect	1 (0.1)	0	0	0
Psychotic disorder	1 (0.1)	0	2 (0.2)	0
Schizoaffective disorder	0	1 (0.1)	0	0
Schizophrenia	0	0	0	1 (0.1)
Homicidal Ideation[b]	**0**	**0**	**0**	**0**

Table 13. Components of the Primary NPS AE Endpoint, Including Preferred Terms, Psychiatric History Cohort

Component Preferred Term	Number (%) of Subjects Varenicline (N=1026)	 Bupropion (N=1017)	 NRT (N=1016)	 Placebo (N=1015)
Suicidal Behavior[b]	**1 (0.1)**	**1 (0.1)**	**0**	**1 (0.1)**
Intentional self-injury	1 (0.1)	0	0	0
Suicide attempt	0	1 (0.1)	0	1 (0.1)
Suicidal Ideation[b]	**5 (0.5)**	**2 (0.2)**	**4 (0.4)**	**2 (0.2)**
Suicidal ideation	5 (0.5)	2 (0.2)	4 (0.4)	2 (0.2)
Suicide[b]	**0**	**0**	**0**	**0**

a. AE severity= Severe only.
b. AE severity=Moderate and Severe only.
MedDRA=Medical Dictionary for Regulatory Activities; NPS AE=neuropsychiatric adverse event; N=number of subjects per treatment arm; NRT=nicotine replacement therapy.
Subjects were counted only once per treatment in each row but could be counted in multiple rows.
Includes all subjects who received at least 1 partial dose of study treatment.
MedDRA (v18.0).

In both the non-PHx and PHx cohorts, agitation (moderate to severe) was the most frequently reported NPS AE component for all treatment arms including varenicline, and because of low number of events in other components, was the only component to which the logistic regression model could be applied. As confirmed by the model, within each cohort rates were similar across treatment arms and ranged from 1.0% to 1.9% in the non-PHx cohort and 2.1% to 2.9% in the PHx cohort. The coded PTs under agitation included Agitation, Disturbance in attention, and Restlessness.

The other NPS AE components were generally reported more frequently in the PHx cohort than in the non-PHx cohort for all treatment arms. Because these components were reported at low rates overall, differences between treatment arms were small. In the PHx cohort the component with largest difference between varenicline and placebo was aggression (1.4% vs 0.8%, respectively, and 0.9% for bupropion and 0.7% for NRT). AEs in this component most frequently coded to the PT Anger. A subject level analysis of the events in the aggression component showed that most were rated by the Investigator as moderate in severity, none resulted in a hospitalization, 2 or less per treatment arm led to treatment discontinuation and most were verbal or thoughts of aggression rather than a physical act.

Although the rates of NPS events in the suicidal behavior and suicide components showed no interpretable treatment differences because the rates were so low, these events are of particular importance because of the potential for imminent self-harm. The single completed suicide in the study occurred in the non-PHx cohort placebo group; the subject left a suicide note that described stressful life situations. In the non-PHx cohort, suicidal behavior (Suicide attempt) was reported in 1 bupropion and 1 NRT subject, the events were considered severe and moderate, respectively, and neither resulted in hospitalization. For the bupropion subject the event occurred 26 days after study treatment had been stopped and was considered related to family conflict and for the NRT subject the event resulted in treatment discontinuation and was considered due to study drug. In the PHx cohort, 3 subjects had NPS endpoint events in

the suicidal behavior component; 1 intentional self-injury in a varenicline subject and 1 suicide attempt in a bupropion and a placebo subject. All 3 events were considered severe and both the varenicline and placebo subject were hospitalized due to the event. For the varenicline subject the event occurred 21 days after the complete course of treatment had ended and was considered non-suicidal by the investigator and due to panic, for the bupropion subject the event occurred 1 day after the complete course of treatment had ended and was considered due to schizoaffective disorder, and for the placebo subject the event resulted in permanent discontinuation of treatment and was considered due to acute psychosocial reasons.

2.4.2.2. Severe-Only NPS AEs in the Primary Endpoint

Another secondary analysis evaluated NPS AE endpoint events that were rated as severe ("severe-only"), ie, those AEs that the Investigator assessed as interfering significantly with the subject's usual function. Due to data sparseness, the analysis based on the generalized linear model for severe-only NPS AEs in the primary endpoint, by cohort, could not be performed. The observed rates of the severe-only NPS AEs and components for which ≥2 subjects reported events are shown in Table 14.

Table 14. Components of the Observed Severe-Only NPS AE Endpoint Reported by ≥2 Subjects in any Treatment Arm, by Cohort

	Number (%) of Subjects			
Non-Psychiatric Cohort	**Varenicline (N=990)**	**Bupropion (N=989)**	**NRT (N=1006)**	**Placebo (N=999)**
Severe-only NPS Endpoint Overall	**1 (0.1)**	**4 (0.4)**	**3 (0.3)**	**5 (0.5)**
Agitation	0	0	2 (0.2)	0
Anxiety	0	1 (0.1)	0	3 (0.3)

	Number (%) of Subjects			
Psychiatric Cohort	**Varenicline (N=1026)**	**Bupropion (N=1017)**	**NRT (N=1016)**	**Placebo (N=1015)**
Severe-only NPS Endpoint Overall	**14 (1.4)**	**14 (1.4)**	**14 (1.4)**	**13 (1.3)**
Agitation	1 (0.1)	1 (0.1)	4 (0.4)	2 (0.2)
Anxiety	5 (0.5)	4 (0.4)	6 (0.6)	2 (0.2)
Depression	6 (0.6)	4 (0.4)	7 (0.7)	6 (0.6)
Mania	2 (0.2)	1 (0.1)	0	0

NPS=neuropsychiatric; AE= adverse event; N=number of subjects per treatment arm; NRT=nicotine replacement therapy.
Subjects were counted only once per treatment in each row but could be counted in multiple rows.
Includes all subjects who received at least 1 partial dose of study treatment.
MedDRA (v18.0)

In the non-PHx cohort the observed rate of severe-only NPS AE endpoint events was low across treatment arms and lowest in varenicline (0.1%) and highest in placebo (0.5%). The rate of severe only NPS AEs was higher in the PHx cohort than in the non-PHx cohort across all 4 treatment arms. In the PHx cohort, the rates for varenicline and the other active treatment arms were the same (1.4%) and similar to placebo (1.3%). These results suggest

that the small numerical differences seen in the overall NPS AE endpoint are driven by events of moderate severity.

2.4.2.3. Further Analysis of the NPS AE Endpoint

The NPS AE endpoint was further evaluated in a descriptive exploratory analysis to look at specific categories of events including:

- Events considered severe in intensity (as presented above),
- Events that met SAE criteria, and
- Events that led to permanent treatment discontinuation.

Table 15 shows a summary of observed rates of these categories of NPS AE endpoint events.

Table 15. Subsets of the NPS AE Primary Endpoint, by Cohort

	Varenicline	Bupropion	NRT	Placebo
Non-psychiatric history cohort	**N=990**	**N=989**	**N=1006**	**N=999**
NPS AE Endpoint n (%)	13 (1.3)	22 (2.2)	25 (2.5)	24 (2.4)
Severe only	1 (0.1)	4 (0.4)	3 (0.3)	5 (0.5)
SAEs[a]	0 (0.0)	1 (0.1)	2 (0.2)	3 (0.3)
Led to permanent treatment discontinuation	1 (0.1)	5 (0.5)	7 (0.7)	4 (0.4)
Unique subjects with severe or SAE or permanent treatment discontinuation	2 (0.2)	7 (0.7)	8 (0.8)	10 (1.0)
Psychiatric history cohort	**N=1026**	**N=1017**	**N=1016**	**N=1015**
NPS AE Endpoint n (%)	67 (6.5)	68 (6.7)	54 (5.3)	50 (4.9)
Severe only	14 (1.4)	14 (1.4)	14 (1.4)	13 (1.3)
SAEs[b]	6 (0.6)	5 (0.5)	4 (0.4)	3 (0.3)
Led to permanent treatment discontinuation	17 (1.7)	15 (1.5)	12 (1.2)	15 (1.5)
Unique subjects with severe or SAE or permanent treatment discontinuation	26 (2.5)	21 (2.1)	19 (1.9)	23 (2.3)

a. The SAEs were: bupropion-Suicide attempt; NRT-Suicide attempt, Panic attack; placebo-Suicidal ideation (2), Completed suicide.
b. The SAEs were: varenicline-Suicidal ideation (2), Depression, Hallucination, auditory, Bipolar I disorder, Anxiety disorder plus Intentional self-injury; bupropion-Suicide attempt plus Schizoaffective disorder, Bipolar I disorder (2), Bipolar II disorder, Emotional disorder plus Mental disorder; NRT-Anxiety (2), Depression, Suicidal ideation; placebo-Suicide attempt, Suicidal ideation, Aggression.
AE=adverse event; N=number of subjects per treatment arm; n=number of subjects with observation of interest; NPS AE=neuropsychiatric adverse event; NRT=nicotine replacement therapy; SAE=serious adverse event.
Subjects were counted only once per treatment in each row but could be counted in multiple rows
Includes all subjects who received at least 1 partial dose of study treatment.

This analysis showed that the number of subjects with NPS AEs in these categories was low overall and was generally similar for varenicline versus placebo, indicating that the small numerical difference in the rates of the primary NPS AE composite endpoint for varenicline versus placebo in the psychiatric cohort was not due to severe events, SAEs or events that led to permanent treatment discontinuation.

An additional analysis evaluated NPS endpoint AEs that resulted in permanent or temporary study drug discontinuation to determine how many of the events resolved upon drug discontinuation, ie, positive dechallenge. The results of this analysis are shown in Table 16.

Table 16. NPS Endpoint Adverse Events Leading to Study Drug Discontinuation: Dechallenge Outcomes, by Cohort

	Varenicline	Bupropion	NRT	Placebo
Non-psychiatric cohort	**N=990**	**N=989**	**N=1006**	**N=999**
Total number of subjects reporting an NPS event	13	22	25	24
Temporary or permanent discontinuations[a]	2	4	3	4
Positive dechallenge	1	2	2	4
Negative dechallenge	1	2	1	0
Psychiatric cohort	**N=1026**	**N=1017**	**N=1016**	**N=1015**
Total number of subjects reporting an NPS event	67	68	54	50
Temporary or permanent discontinuations[a]	13	13	10	13
Positive dechallenge	5	10	4	9
Negative dechallenge	8	3	6	4

a. does not include discontinuations where AE resolution occurred prior to de-challenge, or subject received concomitant medication to treat AE.
Decision for positive dechallenge based on resolution of AE within 5 half-lives of varenicline (ie, 5 days given $t_{1/2}$ of 24 hours)

The number of subjects with NPS endpoint events that could be assessed for dechallenge was low in the non-PHx cohort. In the PHx cohort the numbers were similar across treatment groups. There was 1 positive dechallenge for varenicline observed in the non-PHx cohort compared to 4 for placebo, and 5 positive dechallenges for varenicline observed in the PHx cohort compared to 9 for placebo. The presence of positive dechallenge outcomes in the placebo treatment arm in greater numbers to those reported for varenicline suggests that these events may be episodic in nature and/or related to the underlying condition or the cessation attempt itself and unlikely to be related to study treatment and illustrates the difficulty in interpreting similar events in the postmarketing setting.

Positive rechallenges, cases in which the event re-emerged when drug was restarted, were few, 1 placebo subject in each cohort, and none reported for the other treatment groups, again highlighting the difficulty in interpreting rechallenge information in the postmarketing setting.

2.4.2.4. Multiple NPS AE Events for the NPS AE Primary Endpoint

The analyses presented above were based on subject level data. It is possible that although differences across treatment arms in the numbers of subjects reporting NPS endpoint events were small, there could have been treatment differences in the number of events reported per

subjects. The results of the analysis of the number of NPS AE events reported per subject are shown in Table 17 for the non-PHx cohort and Table 18 for the PHx cohort. Multiple events could be reports of the same event by the same subject over a discrete period of time, or a different event but within or across the same component.

Table 17. Multiple Events Summary for the NPS AE Primary Endpoint, Non-Psychiatric History Cohort

	Varenicline (N=990)	Bupropion (N=989)	NRT (N=1006)	Placebo (N=999)
Number of Subjects with NPS AE	13	22	25	24
Individual AE Event Assessment				
Total Number of NPS AE events	17	28	32	26
Number (%) of Subjects				
with 1 NPS AE event	9 (69.2)	18 (81.8)	20 (80.0)	22 (91.7)
with >1 NPS AE event	4 (30.8)	4 (18.2)	5 (20.0)	2 (8.3)
with NPS AE events in more than 1 NPS AE Component	2 (15.4)	2 (9.1)	5 (20.0)	2 (8.3)

AE=adverse event; NPS =neuropsychiatric; N=number of subjects in treatment group; NRT=nicotine replacement therapy.
Includes all subjects who received at least 1 partial dose of study treatment.
Percentages are calculated based on the number of subjects with an NPS AE.
MedDRA (v18.0)

Table 18. Multiple Events Summary for the NPS AE Primary Endpoint, Psychiatric History Cohort

	Varenicline (N=1026)	Bupropion (N=1017)	NRT (N=1016)	Placebo (N=1015)
Number of Subjects with NPS AE	67	68	54	50
Individual AE Event Assessment				
Total Number of NPS AE events	89	88	72	61
Number (%) of Subjects				
with exactly 1 NPS AE event	51 (76.1)	51 (75.0)	41 (75.9)	40 (80.0)
with >1 NPS AE event	16 (23.9)	17 (25.0)	13 (24.1)	10 (20.0)
with NPS AE event in more than 1 NPS AE Component	12 (17.9)	12 (17.6)	10 (18.5)	9 (18.0)

AE=adverse event; NPS =neuropsychiatric; N=number of subjects in treatment group; NRT=nicotine replacement therapy.
Includes all subjects who received at least 1 partial dose of study treatment.
Percentages are calculated based on the number of subjects with an NPS AE.
MedDRA (v18.0)

In both the non-PHx and PHx cohorts, the majority of subjects reporting NPS AE endpoint events reported only 1 event. In the non-PHx cohort, a higher percentage of varenicline subjects with at least 1 NPS AE (30.8%) reported more than 1 event compared to placebo (8.3%) and the other treatment arms (bupropion 18.2%, placebo 20%); however, the number of subjects is small overall. In the PHx cohort, the percentage of subjects with at least 1 NPS AE who reported multiple events was similar across treatment arms (varenicline 23.9%, bupropion 25.0%, NRT 24.1%, placebo 20.0%).

2.4.2.5. Observed Composite NPS AE Rates by Sub-Cohort

A further analysis of the PHx cohort was performed to explore whether NPS endpoint AEs were differentially reported in subjects with one type of psychiatric disorder versus another. Table 19 shows the observed rate of NPS AE endpoint for the sub-cohorts of the psychiatric history cohort.

Table 19. Observed Rate for the Treatment-Emergent Composite NPS AE Endpoint by Cohort and by Sub-Cohort for the Psychiatric History Cohort

	Varenicline n/N (%)	Bupropion n/N (%)	NRT n/N (%)	Placebo n/N (%)
Psychiatric History (total)	67/1026 (6.5)	68/1017 (6.7)	54/1016 (5.3)	50/1015 (4.9)
Primary diagnosis cataegory				
Mood disorder	50/731 (6.8)	46/716 (6.4)	40/713 (5.6)	33/722 (4.6)
Anxiety disorder	11/193 (5.7)	16/200 (8.0)	9/195 (4.6)	11/194 (5.7)
Psychotic disorder	6/95 (6.3)	6/96 (6.3)	5/99 (5.1)	6/96 (6.3)
Borderline personality disorder	0/7	0/5	0/9	0/3

N=number of subjects in treatment group; n=number of subjects with disorder; NPS AE=neuropsychiatric adverse event; NRT=nicotine replacement therapy.
Includes all subjects who received at least 1 partial dose of study treatment.

The percentage of subjects with anxiety disorders and psychotic disorders who reported NPS AE endpoints were the same for varenicline and placebo (5.7% and 6.3%, respectively). A slightly higher percentage of varenicline subjects (6.8%) with mood disorders reported events than placebo subjects with mood disorders (4.6%). Differences among the other treatment arms were also small.

2.4.2.6. Primary NPS AE Endpoint by Smoking Status

Post hoc exploratory analyses of the primary NPS AE endpoint data evaluated the potential association between NPS AEs and nicotine withdrawal symptoms brought on by abstinence from smoking using data from the weekly Nicotine Use Inventory (NUI). None of these analyses showed a clear relationship between abstinence or continuing to smoke and the occurrence of these AEs at the study or cohort level, although a potential role of abstinence cannot be ruled out for some subjects reporting NPS AEs.

The results of 1 of the analyses which plotted the week of onset of NPS AEs, did not show any particular differences in temporal association of events across treatment groups, notably, including placebo.

2.4.2.7. Analysis of Other Psychiatric Assessments

2.4.2.7.1. Columbia Suicide Severity Rating Scale

The C-SSRS provided additional insight into suicide-related events beyond what was reported as AEs. The C-SSRS was administered at Screening, Baseline and at each weekly in-clinic visit throughout the study. The results for the Screening visit, which was a lifetime look-back, and the treatment-emergent period are summarized in Table 20.

Table 20. Number of Subjects with Positive Responses on the Columbia-Suicide Severity Rating Scale: Lifetime and Treatment-Emergent by Cohort

	Varenicline	Bupropion	NRT	Placebo
Non-Psychiatric Cohort				
Screening (Lifetime)				
Number Assessed	990	989	1006	999
Suicidal Behavior	6 (0.6)	9 (0.9)	7 (0.7)	6 (0.6)
Suicidal Ideation	48 (4.8)	43 (4.3)	50 (5.0)	49 (4.9)
Self-Injurious Behavior, no Suicidal Intent	0	3 (0.3)	6 (0.6)	7 (0.7)
Treatment-Emergent				
Number Assessed	988	983	996	995
Suicidal Behavior or/and Ideation[a]	7 (0.7)	4 (0.4)	3 (0.3)	7 (0.7)
Suicidal Behavior[a]	0	0[a]	1 (0.1)	1 (0.1)
Suicidal Ideation[a]	7 (0.7)	4 (0.4)	3 (0.3)	6 (0.6)
Self-Injurious Behavior, no Suicidal Intent	0	0	0	0
Psychiatric Cohort				
Screening (Lifetime)				
Number Assessed	1026	1017	1016	1015
Suicidal Behavior	137 (13.4)	143 (14.1)	111 (10.9)	123 (12.1)
Suicidal Ideation	338 (32.9)	357 (35.1)	333 (32.8)	349 (34.4)
Self-Injurious Behavior, no Suicidal Intent	44 (4.3)	45 (4.4)	33 (3.2)	36 (3.5)
Treatment-Emergent				
Number Assessed	1017	1012	1006	1006
Suicidal Behavior or/and Ideation[a]	27 (2.7)	15 (1.5)	20 (2.0)	25 (2.5)
Suicidal Behavior[a]	0	1 (0.1)	0	2 (0.2)
Suicidal Ideation[a]	27 (2.7)	15 (1.5)	20 (2.0)	25 (2.5)
Self-Injurious Behavior, no Suicidal Intent	2 (0.2)	1 (0.1)	0	1 (0.1)

a. For this analysis, the time frame assigned for the positive response was based solely on the collection date of the instrument. Using a revised more conservative reporting timeframe for data collected after the last treatment dose+30 days, 3 subjects with reports of suicidal behavior (non-psychiatric cohort - 1 bupropion; psychiatric cohort - 1 varenicline and 1 NRT) and 18 subjects with reports of suicidal ideation (non-psychiatric cohort – 2 varenicline, 1 bupropion, 2 NRT, 1 placebo; psychiatric cohort – 3 varenicline, 2 bupropion, 4 NRT, 3 placebo) shift from the follow-up to the treatment-emergent period. The 3 subjects with behavior also had ideation and thus they represent a subset of the 18 subjects with ideation. These 18 subjects are not reflected in the table.
NRT=nicotine replacement therapy.
Lifetime=lifetime look-back from screening.
Treatment Emergent: during treatment plus 30 days.
Includes all subjects who received at least 1 partial dose of study treatment.

The rates of positive responses for suicidal behavior and/or ideation on the C-SSRS for the Lifetime and Treatment emergent periods were similar across all treatment arms within each cohort, however, as would be expected, the rates were higher in the PHx cohort compared to the non-PHx cohort.

Whether or not positive responses on the C-SSRS were considered to be AEs was based on the judgment of the Investigator and therefore, it is not expected that the number of C-SSRS positive responses would match the numbers of AEs in the High Level Group Term (HLGT) Suicidal and self-injurious behaviors, not elsewhere classified (NEC). Treatment-emergent

AEs coding to the HLGT Suicidal and self-injurious behaviors NEC are shown in Table 21 below. There was no reconciliation of the C-SSRS and AE data.

Table 21. Adverse Events in the Suicidal and Self-Injurious Behaviours NEC High Level Group Term, by Cohort

Suicidal and self-injurious behaviours NEC Preferred Term	Number (%) of Subjects Varenicline	Bupropion	NRT	Placebo
Non-Psychiatric History	N=990	N=989	N=1006	N=999
Suicidal ideation	2 (0.2)[a]	2 (0.2)[b]	2 (0.2)	3 (0.3)
Suicide attempt	0	1 (0.1)	1 (0.1)	0
Completed suicide	0	0	0	1 (0.1)
Psychiatric History	N=1026	N=1017	N-1016	N=1015
Suicidal ideation	8 (0.8)[c]	3 (0.3)[b]	7 (0.7)[c]	7 (0.7)[d]
Suicidal behavior	0	0	0	1 (0.1)[b]
Suicide attempt	0	1(0.1)	0	1 (0.1)

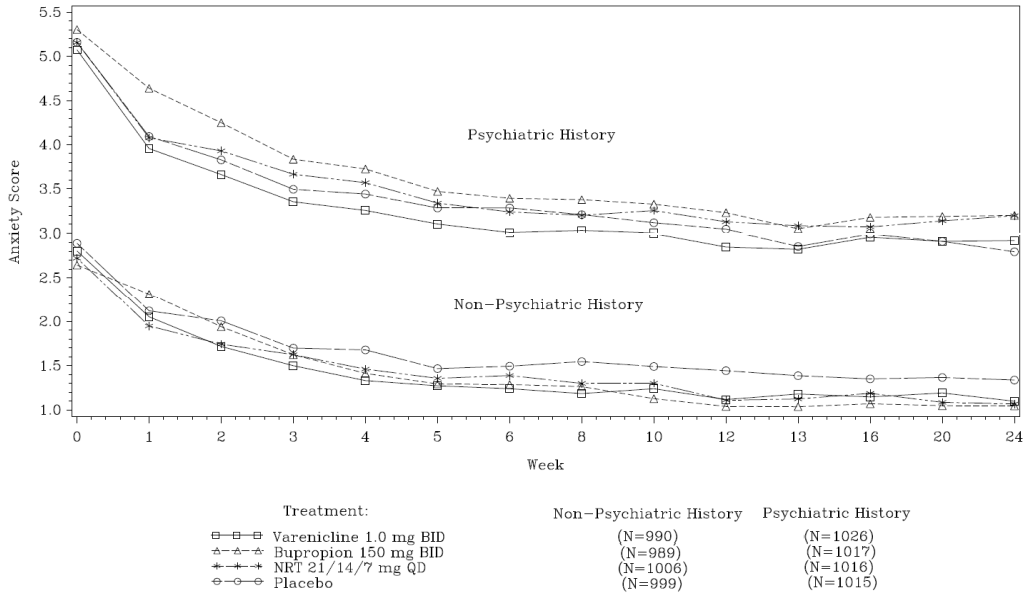
a. 2 events rated as mild.
b. 1 event rated as mild.
c. 3 events rated as mild.
d. 5 events rated as mild.
NEC=not elsewhere classified; NRT=nicotine replacement therapy.
Includes all subjects who received at least 1 partial dose of study treatment.
MedDRA v18.0

The number of subjects reporting AEs in the HLGT Suicidal and self-injurious behaviours NEC, was low overall, but slightly higher in the PHx cohort compared to the non-PHx cohort. Differences between treatment arms were small. Note that events rated as mild were not included in the primary NPS AE endpoint.

2.4.2.7.2. Hospital Anxiety and Depression Scale

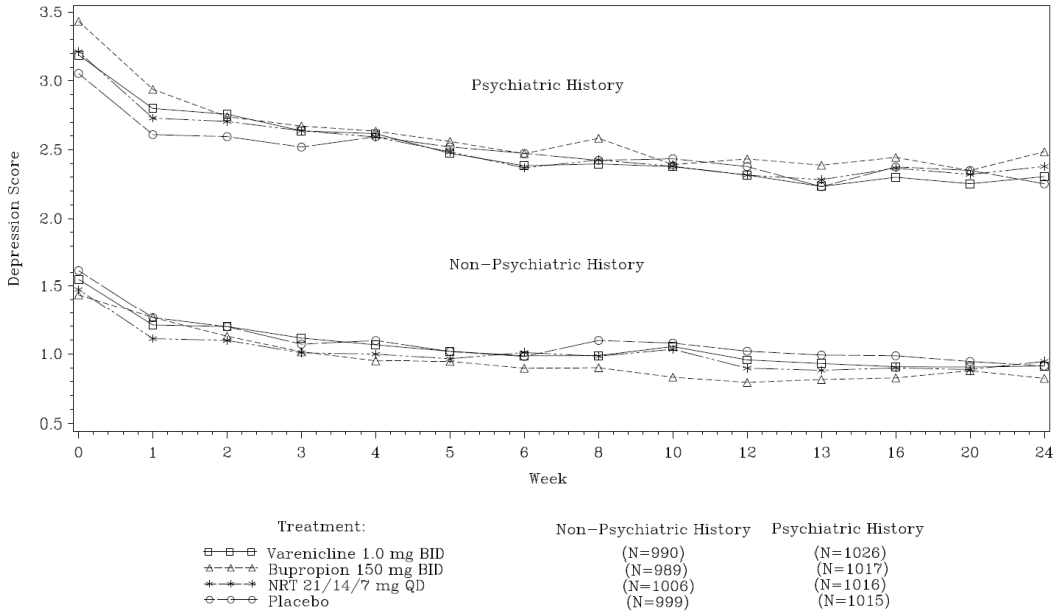
The HADS is a commonly used, self-assessment scale to determine the levels of anxiety and depression. Scoring, as described in Section 2.4.1.2 is interpreted as: 0-7 = normal, 8-10 = suggestive, 11-21 = probable. Data from the HADS are summarized Figure 5 for the anxiety subscale and Figure 6 for the Depression subscale.

Figure 5. Hospital Anxiety and Depression Scale, Anxiety Mean Score, by Visit and Cohort



BID=twice daily; N=total number of subjects per treatment arm; NRT=nicotine replacement therapy; QD=once daily.
Includes all subjects who received at least 1 partial dose of study treatment.

Figure 6. Hospital Anxiety and Depression Scale, Depression Mean Score, by Visit and Cohort



BID=twice daily; N=total number of subjects per treatment arm; NRT=nicotine replacement therapy; QD=once daily.
Includes all subjects who received at least 1 partial dose of study treatment.

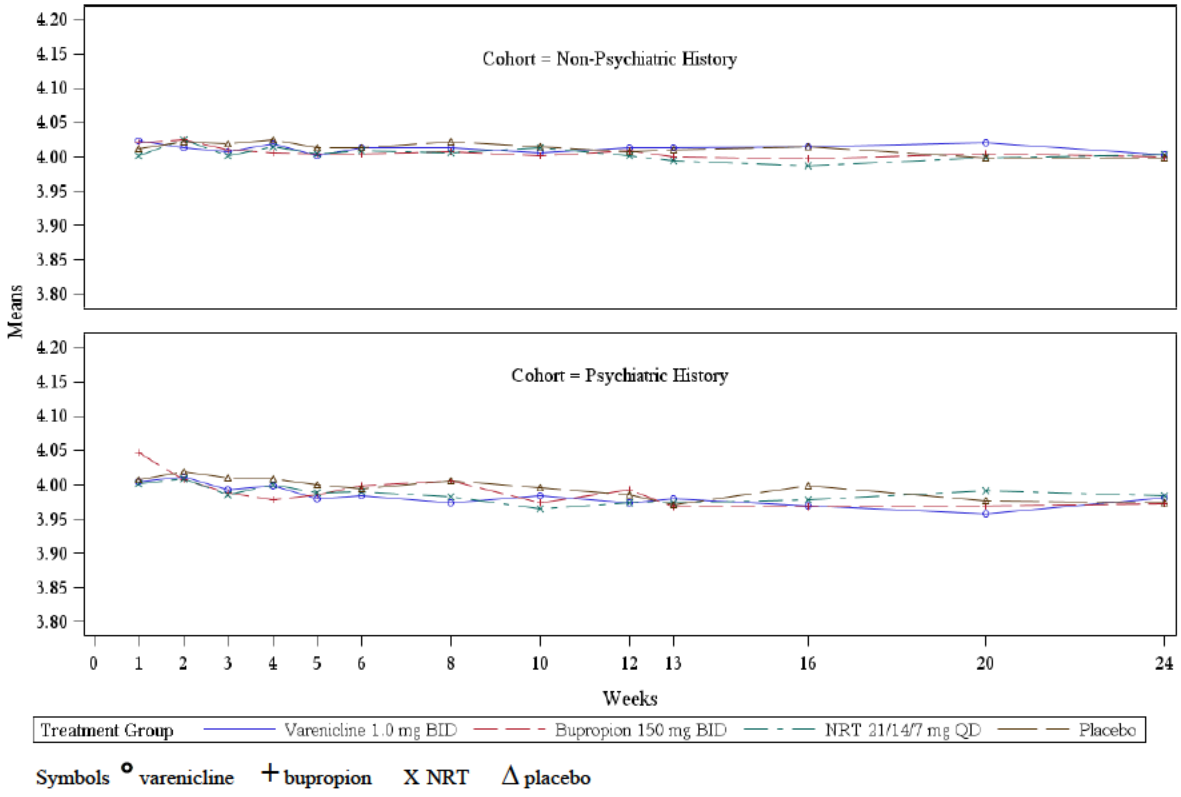
HADS sub-scale scores for both anxiety and depression were higher at baseline among subjects in the PHx cohort compared to subjects in the non-PHx cohort for all treatment arms.

Over the first 12 weeks of the study (treatment period), mean scores decline for both sub-scales in all treatment arms, indicating slight improvement in anxiety and depression. Over the second 12 weeks of the study (non-treatment follow-up period), mean scores were either stable or showed a slight further decline.

2.4.2.7.3. Clinical Global Impression of Improvement

The CGI-I is a clinician rated instrument that measures change in subject's psychiatric condition (or lack thereof in the stratum without psychiatric disorders) on a 7 point scale. As noted in Section 2.4.1.2, scores are interpreted as 4 being no change, 1 to 3 being levels of improvement, and 5 to 7 being levels of worsening. Data from the CGI-I are summarized in Figure 7.

Figure 7. Clinical Global Impression of Improvement Total Score, by Visit and Cohort



BID=twice daily; NRT=nicotine replacement therapy; QD=once daily.
Includes all subjects who received at least 1 partial dose of study treatment.

For varenicline subjects as well as subjects in the other treatment arms, the majority of subjects who were assessed during the first 12 weeks on treatment showed no change in the CGI-I as assessed relative to their psychiatric status. This trend continued during the 12 weeks of non-treatment follow-up.

2.4.2.8. General Adverse Event Data

The sections below provide a summary of all-causality, treatment-emergent AEs reported in EAGLES. AEs occurring before the start of study medication and post-treatment-emergent events, those occurring more than 30 days after the last dose of study medication, are not included.

2.4.2.8.1. Overview of Adverse Events

Table 22 provides an overview of the treatment-emergent AEs for the study overall and by cohort.

Table 22. Overview of Treatment-Emergent Adverse Events, Overall and by Cohort

	Number (%) of Subjects			
	Varenicline	**Bupropion**	**NRT**	**Placebo**
Overall				
Subjects Evaluable for AEs	2016	2006	2022	2014
Subjects with AEs	1503 (74.6)	1446 (72.1)	1436 (71.0)	1345 (66.8)
Subjects with SAEs	39 (1.9)	48 (2.4)	46 (2.3)	41 (2.0)
Subjects with Severe AEs	106 (5.3)	99 (4.9)	112 (5.5)	89 (4.4)
Subjects Discontinued Due to AEs	166 (8.2)	176 (8.8)	162 (8.0)	122 (6.1)
Subjects with Dose Reduced or Temporary Discontinuation Due to AEs	164 (8.1)	143 (7.1)	163 (8.1)	112 (5.6)
Non-Psychiatric Cohort				
Subjects Evaluable for AEs	990	989	1006	999
Subjects with AEs	720 (72.7)	704 (71.2)	698 (69.4)	649 (65.0)
Subjects with SAEs	16 (1.6)	19 (1.9)	21 (2.1)	16 (1.6)
Subjects with Severe AEs	45 (4.5)	28 (2.8)	46 (4.6)	35 (3.5)
Subjects Discontinued Due to AEs	57 (5.8)	75 (7.6)	74 (7.4)	29 (2.9)
Subjects with Dose Reduced or Temporary Discontinuation Due to AEs	74 (7.5)	73 (7.4)	89 (8.8)	52 (5.2)
Psychiatric Cohort				
Subjects Evaluable for AEs	1026	1017	1016	1015
Subjects with AEs	783 (76.3)	742 (73.0)	738 (72.6)	696 (68.6)
Subjects with SAEs	23 (2.2)	29 (2.9)	25 (2.5)	25 (2.5)
Subjects with Severe AEs	61 (5.9)	71 (7.0)	66 (6.5)	54 (5.3)
Subjects Discontinued Due to AEs	109 (10.6)	101 (9.9)	88 (8.7)	93 (9.2)
Subjects with Dose Reduced or Temporary Discontinuation Due to AEs	90 (8.8)	70 (6.9)	74 (7.3)	60 (5.9)

AE=adverse event; NRT=nicotine replacement therapy; SAE=serious adverse event.
Treatment-emergent adverse events included the interval from first date of study drug to last date of study drug plus 30 days.
Subjects were counted only once per treatment in each row but could be counted in multiple rows.
SAEs - according to the Investigator's assessment.
Includes all subjects who received at least 1 partial dose of study treatment.
MedDRA v18.0

In the non-PHx cohort, 2771 (69.6%) of the 3984 subjects evaluable for AEs experienced an AE, 72 subjects (1.8%) had an SAE, and 235 subjects (5.9%) discontinued study drug due to AEs. The percentage of subjects with these types of AEs were similar across active treatment arms but were lower in the placebo group, except for SAEs for which the percentages were similar across all treatment arms.

In the PHx cohort, 2959 (72.6%) of the 4074 subjects evaluable for AEs experienced an AE, 102 subjects (2.5%) had an SAE, and 391 subjects (9.6%) discontinued study drug due to AEs, all slightly higher percentages than in the non-PHx cohort. As in the non-PHx cohort, the percentages of subjects with these types of AEs were similar across active treatment arms but were lower in the placebo group, except for SAEs for which the percentages were similar across all treatment arms.

2.4.2.8.2. Common Treatment-Emergent Adverse Events (All Causalities)

Table 23, Table 24 and Table 25 provide summaries of the most frequent treatment-emergent AEs (ie, AEs reported by ≥5% of subjects in any treatment arm) for the study overall, the non-PHx cohort and PHx cohort, respectively.

Table 23. Most Frequently Reported Treatment-Emergent Adverse Events (≥5% of Subjects in any Treatment Arm), Study Overall

System Organ Class Preferred Term	Study Overall			
	Varenicline (N=2016)	Bupropion (N=2006)	NRT (N=2022)	Placebo (N=2014)
Subjects with Adverse Events	**1503 (74.6)**	**1446 (72.1)**	**1436 (71.0)**	**1345 (66.8)**
Gastrointestinal Disorders	786 (39.0)	527 (26.3)	481 (23.8)	414 (20.6)
Nausea	511 (25. 3)	201 (10.0)	199 (9.8)	137 (6.8)
Dry mouth	66 (3.3)	146 (7.3)	59 (2.9)	64 (3.2)
General Disorders And Administration Site Conditions	270 (13.4)	241 (12.0)	404 (20.0)	229 (11.4)
Application site pruritus	22 (1.1)	12 (0.6)	109 (5.4)	16 (0.8)
Fatigue	124 (6.2)	57 (2.8)	75 (3.7)	83 (4.1)
Infections And Infestations	533 (26.4)	475 (23.7)	495 (24.5)	506 (25.1)
Nasopharyngitis	174 (8.6)	156 (7.8)	126 (6.2)	135 (6.7)
Upper respiratory tract infection	109 (5.4)	104 (5.2)	97 (4.8)	115 (5.7)
Nervous System Disorders	440 (21.8)	440 (21.9)	443 (21.9)	374 (18.6)
Headache	245 (12.2)	186 (9.3)	233 (11.5)	199 (9.9)
Psychiatric Disorders	720 (35.7)	767 (38.2)	722 (35.7)	613 (30.4)
Anxiety	132 (6.5)	169 (8.4)	138 (6.8)	120 (6.0)
Irritability	82 (4.1)	71 (3.5)	108 (5.3)	104 (5.2)
Abnormal dreams	201 (10.0)	131 (6.5)	251 (12.4)	92 (4.6)
Insomnia	189 (9.4)	245 (12.2)	196 (9.7)	139 (6.9)

N=total number of subjects per treatment arm; NRT=nicotine replacement therapy.
Subjects are only counted once per treatment for each row but may be counted in multiple rows.
Includes all subjects who received at least 1 partial dose of study treatment.
Treatment-emergent=during treatment plus 30 days.
MedDRA v18.0

Table 24. Most Frequently Reported Treatment-Emergent Adverse Events (≥5% of Subjects in any Treatment Arm), Non-Psychiatric History Cohort

System Organ Class Preferred Term	Non-Psychiatric History			
	Varenicline (N=990)	Bupropion (N=989)	NRT (N=1006)	Placebo (N=999)
Subjects with Adverse Events	**720 (72.7)**	**704 (71.2)**	**698 (69.4)**	**649 (65.0)**
Gastrointestinal Disorders	379 (38.3)	234 (23.7)	233 (23.2)	190 (19.0)
Nausea	243 (24.5)	90 (9.1)	95 (9.4)	63 (6.3)
Dry mouth	29 (2.9)	70 (7.1)	31 (3.1)	26 (2.6)
General Disorders And Administration Site Conditions	110 (11.1)	110 (11.1)	191 (19.0)	94 (9.4)
Application site pruritus	11 (1.1)	6 (0.6)	51 (5.1)	11 (1.1)
Infections And Infestations	263 (26.6)	241 (24.4)	240 (23.9)	254 (25.4)
Nasopharyngitis	86 (8.7)	79 (8.0)	65 (6.5)	73 (7.3)

Table 24. Most Frequently Reported Treatment-Emergent Adverse Events (≥5% of Subjects in any Treatment Arm), Non-Psychiatric History Cohort

System Organ Class Preferred Term	Non-Psychiatric History			
	Varenicline (N=990)	Bupropion (N=989)	NRT (N=1006)	Placebo (N=999)
Upper respiratory tract infection	47 (4.7)	48 (4.9)	40 (4.0)	55 (5.5)
Nervous System Disorders	206 (20.8)	199 (20.1)	225 (22.4)	162 (16.2)
Headache	116 (11.7)	87 (8.8)	129 (12.8)	95 (9.5)
Dizziness	33 (3.3)	51 (5.2)	38 (3.8)	28 (2.8)
Psychiatric Disorders	315 (31.8)	332 (33.6)	301 (29.9)	259 (25.9)
Anxiety	46 (4.6)	64 (6.5)	45 (4.5)	57 (5.7)
Abnormal dreams	83 (8.4)	47 (4.8)	111 (11.0)	39 (3.9)
Insomnia	95 (9.6)	126 (12.7)	91 (9.0)	73 (7.3)

N=total number of subjects per treatment arm; NRT=nicotine replacement therapy.
Subjects are only counted once per treatment for each row but may be counted in multiple rows.
Includes all subjects who received at least 1 partial dose of study treatment.
Treatment-emergent=during treatment plus 30 days
MedDRA v18.0

Table 25. Most Frequently Reported Treatment-Emergent Adverse Events (≥5% of Subjects in any Treatment Arm), Psychiatric History Cohort

System Organ Class Preferred Term	Psychiatric History			
	Varenicline (N=1026)	Bupropion (N=1017)	NRT (N=1016)	Placebo (N=1015)
Subjects with Adverse Events	**783 (76.3)**	**742 (73.0)**	**738 (72.6)**	**696 (68.6)**
Gastrointestinal Disorders	407 (39.7)	293 (28.8)	248 (24.4)	224 (22.1)
Nausea	268 (26.1)	111 (10.9)	104 (10.2)	74 (7.3)
Dry mouth	37 (3.6)	76 (7.5)	28 (2.8)	38 (3.7)
General Disorders And Administration Site Conditions	160 (15.6)	131 (12.9)	213 (21.0)	135 (13.3)
Application site pruritus	11 (1.1)	6 (0.6)	58 (5.7)	5 (0.5)
Fatigue	85 (8.3)	37 (3.6)	47 (4.6)	59 (5.8)
Infections And Infestations	270 (26.3)	234 (23.0)	255 (25.1)	252 (24.8)
Nasopharyngitis	88 (8.6)	77 (7.6)	61 (6.0)	62 (6.1)
Upper respiratory tract infection	62 (6.0)	56 (5.5)	57 (5.6)	60 (5.9)
Nervous System Disorders	234 (22.8)	241 (23.7)	218 (21.5)	212 (20.9)
Headache	129 (12.6)	99 (9.7)	104 (10.2)	104 (10.2)
Psychiatric Disorders	405 (39.5)	435 (42.8)	421 (41.4)	354 (34.9)
Agitation	47 (4.6)	56 (5.5)	39 (3.8)	41 (4.0)
Anxiety	86 (8.4)	105 (10.3)	93 (9.2)	63 (6.2)
Depressed mood	47 (4.6)	47 (4.6)	52 (5.1)	52 (5.1)
Irritability	48 (4.7)	42 (4.1)	61 (6.0)	67 (6.6)
Abnormal dreams	118 (11.5)	84 (8.3)	140 (13.8)	53 (5.2)
Insomnia	94 (9.2)	119 (11.7)	105 (10.3)	66 (6.5)

N=total number of subjects per treatment arm; NRT=nicotine replacement therapy.
Subjects are only counted once per treatment for each row but may be counted in multiple rows.
Includes all subjects who received at least 1 partial dose of study treatment.
Treatment-emergent=during treatment plus 30 days.
MedDRA v18.0

In both cohorts, common AEs were generally similar across treatment arms and for the active treatments, were consistent with the known safety profiles of each treatment, eg, high rates of Nausea for varenicline, Abnormal dreams for varenicline and NRT, Application site pruritis for NRT.

An additional analysis of frequent events specifically in the MedDRA Psychiatric disorders System Organ Class is shown in Table 26 for the non-PHx cohort and Table 27 for the PHx cohort; these tables include events reported in ≥1% of subjects in any treatment arm. Although these tables include events terms that were in the NPS AE endpoint, the tables are more inclusive in that they include events of any severity (mild, moderate or severe) rather than those restricted to moderate and/or severe. Those event terms that are included in the NPS AE endpoint and their severity criteria are noted in the tables.

Table 26. Most Frequently Reported Treatment-Emergent Adverse Events in the Psychiatric System Organ Class (≥1% of Subjects in any Treatment Arm), Non-Psychiatric History Cohort

	Varenicline (N = 990)	Bupropion (N = 989)	NRT (N = 1,006)	Placebo (N = 999)
	number (%) of subjects			
Psychiatric disorders SOC	**315 (31.8)**	**332 (33.6)**	**301 (29.9)**	**259 (25.9)**
Abnormal dreams	83 (8.4)	47 (4.8)	111 (11.0)	39 (3.9)
Agitation*	32 (3.2)	29 (2.9)	28 (2.8)	25 (2.5)
Anxiety**	46 (4.6)	64 (6.5)	45 (4.5)	57 (5.7)
Depressed mood**	31 (3.1)	13 (1.3)	27 (2.7)	29 (2.9)
Depression**	17 (1.7)	13 (1.3)	8 (0.8)	15 (1.5)
Initial insomnia	7 (0.7)	6 (0.6)	10 (1.0)	4 (0.4)
Insomnia	95 (9.6)	126 (12.7)	91 (9.0)	73 (7.3)
Irritability	34 (3.4)	29 (2.9)	47 (4.7)	37 (3.7)
Middle insomnia	7 (0.7)	15 (1.5)	13 (1.3)	6 (0.6)
Nervousness**	14 (1.4)	18 (1.8)	11 (1.1)	9 (0.9)
Nightmare	9 (0.9)	7 (0.7)	26 (2.6)	3 (0.3)
Restlessness*	14 (1.4)	14 (1.4)	15 (1.5)	14 (1.4)
Sleep disorder	31 (3.1)	37 (3.7)	17 (1.7)	19 (1.9)
Tension**	2 (0.2)	10 (1.0)	2 (0.2)	2 (0.2)

N=number of subjects treated subjects; NRT=nicotine replacement therapy.
Subjects are only counted once per treatment for each row but may be counted in multiple rows.
Includes all subjects who received at least 1 partial dose of study treatment.
Treatment-emergent includes the interval from first date of study drug to last date of study drug plus 30 days.
* event included in NPS AE endpoint if severity = moderate or severe.
** event included in NPS AE endpoint if severity = severe.
MedDRA v18.0

Table 27. Most Frequently Reported Treatment-Emergent Adverse Events in the Psychiatric System Organ Class (≥1% of Subjects in any Treatment Arm), Psychiatric History Cohort

	Varenicline (N=1026)	Bupropion (N=1017)	NRT (N=1016)	Placebo (N=1015)
	number (%) of subjects			
Psychiatric disorders	**405 (39.5)**	**435 (42.8)**	**421 (41.4)**	**354 (34.9)**
Abnormal dreams	118 (11.5)	84 (8.3)	140 (13.8)	53 (5.2)
Agitation*	47 (4.6)	56 (5.5)	39 (3.8)	41 (4.0)
Anger *	11 (1.1)	4 (0.4)	4 (0.4)	5 (0.5)
Anxiety**	86 (8.4)	105 (10.3)	93 (9.2)	63 (6.2)
Depressed mood**	47 (4.6)	47 (4.6)	52 (5.1)	52 (5.1)
Depression**	49 (4.8)	45 (4.4)	47 (4.6)	46 (4.5)
Depressive symptom**	11 (1.1)	8 (0.8)	12 (1.2)	13 (1.3)
Initial insomnia	15 (1.5)	8 (0.8)	10 (1.0)	2 (0.2)
Insomnia	94 (9.2)	119 (11.7)	105 (10.3)	66 (6.5)
Irritability	48 (4.7)	42 (4.1)	61 (6.0)	67 (6.6)
Major depression**	7 (0.7)	10 (1.0)	5 (0.5)	2 (0.2)
Middle insomnia	11 (1.1)	16 (1.6)	13 (1.3)	8 (0.8)
Nervousness**	21 (2.0)	19 (1.9)	17 (1.7)	27 (2.7)
Nightmare	13 (1.3)	9 (0.9)	31 (3.1)	14 (1.4)
Panic attack*	9 (0.9)	19 (1.9)	13 (1.3)	11 (1.1)
Restlessness*	17 (1.7)	20 (2.0)	14 (1.4)	9 (0.9)
Sleep disorder	34 (3.3)	36 (3.5)	28 (2.8)	23 (2.3)
Tension**	9 (0.9)	5 (0.5)	10 (1.0)	6 (0.6)

N=number of subjects treated subjects; NRT=nicotine replacement therapy.
Subjects are only counted once per treatment for each row but may be counted in multiple rows.
Includes all subjects who received at least 1 partial dose of study treatment.
Treatment-emergent includes the interval from first date of study drug to last date of study drug plus 30 days.
* event included in NPS AE endpoint if severity = moderate or severe.
** event included in NPS AE endpoint if severity = severe.
MedDRA v18.0

In the non-PHx cohorts, the percentages of subjects reporting psychiatric AEs were similar across active treatment arms, although slightly higher for the 3 active treatments compared to placebo (31.8% varenicline, 33.6% bupropion, 29.9% NRT, 25.9% placebo). The largest differences between treatment arms were seen in sleep-related events.

The percentages of subjects reporting psychiatric AEs in the PHx cohort were higher than in the non-PHx cohort for all treatment arms, but the differences between treatment arms were similar to those seen in the non-PHx cohort (39.5% varenicline, 42.8% bupropion, 41.4% NRT, 34.9% placebo). In the PHx cohort, the largest differences between treatment arms were also seen in sleep-related events.

2.4.2.8.3. Deaths

In total, there were 4 treatment-emergent deaths in EAGLES, 2 in the non-PHx cohort and 2 in the PHx cohort. There were no deaths in varenicline subjects.

In the non-PHx cohort, reported deaths included 1 bupropion subject (Overdose) and 1 placebo subject (Completed Suicide). The completed suicide was considered related to study drug by the Investigator; the Overdose was not considered related to study drug. The overdose death was due to a heroin overdose; the subject had a history of illicit drug use including heroin.

In the PHx cohort, reported deaths included 1 bupropion subject (Cardiovascular disorder), and 1 placebo subject (Pulmonary embolism). Neither death was considered treatment related.

2.4.3. Safety Conclusions

The primary safety endpoint was the occurrence of at least 1 treatment-emergent "severe" AE of anxiety, depression, feeling abnormal, or hostility, or at least 1 treatment-emergent "moderate" or "severe" AE of agitation, aggression, delusion, hallucination, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, or suicide. "Treatment-emergent" was defined as during treatment and up to 30 days after last dose of study medication.

The results of the primary NPS AE endpoint analysis showed low observed rates overall, and similar rates across treatment groups: varenicline 4.0%, bupropion 4.5%, NRT 3.9% and placebo 3.7%. In the non-psychiatric cohort, the observed rates of the composite primary NPS AE endpoint were: 1.3% in the varenicline treatment group, 2.2% in bupropion, 2.5% in NRT, and 2.4% in placebo. The rates of the NPS AE endpoint were higher in the psychiatric cohort compared to the non-psychiatric cohort, but were similar across all treatment groups: 6.5% in varenicline, 6.7% in bupropion, 5.3% in NRT, and 4.9% in placebo.

Based on the statistical model, for the study overall all pairwise comparisons involving varenicline, including the primary comparison of varenicline vs placebo, had RDs near or below zero and all 95% CIs included zero, showing no statistically significant increased risk of NPS AEs in the composite endpoint with varenicline treatment. There did appear to be an effect of cohort on the RDs.

Considering the cohorts separately, in the non-PHx cohort all pairwise comparisons involving varenicline, including the primary comparison of varenicline vs placebo, had RDs below zero and 95% CIs below or including zero, showing no increased risk of NPS AEs in the composite endpoint with varenicline treatment in subjects without a history of a psychiatric disorder.

In the PHx cohort, all pairwise comparisons involving varenicline, including the primary comparison of varenicline vs placebo, had RDs above (vs placebo and NRT) or near zero (vs bupropion) and all 95% CIs included zero, showing no statistically significant increased risk of NPS AEs in the composite endpoint with varenicline treatment in subjects with a history of a psychiatric disorder. There were small numerical differences between the treatment arms in the PHx cohort.

The pre-specified secondary endpoint analyses showed that the rates of NPS endpoint AEs that were considered severe in intensity were low and similar across treatment arms,

particularly in the PHx cohort. In both the non-PHx cohort and the PHx cohort, agitation (moderate or severe) was the only component that occurred with sufficient frequency to allow statistical analysis, and this component showed no differences between treatment arms in either cohort. In the PHx cohort, aggression was the component with the largest treatment differences between varenicline and placebo and these differences were primarily in the PT Anger, which was reported by 0.8% of varenicline subjects and 0.4% of placebo subjects. Further analysis of the events in the aggression component showed no treatment differences in the characterization of the individual events, few involved actual physical aggression and few resulted in hospitalization or treatment discontinuation.

A descriptive exploratory analysis was conducted, to ascertain whether the small numerical difference in the rates of the primary NPS AE composite endpoint seen in the varenicline versus placebo arms in the psychiatric cohort were driven by the AEs that were (1) rated as severe in intensity by Investigators (as discussed above), were SAEs by the regulatory criteria (eg, events that result in death or are life threatening, lead to hospitalization (initial or prolonged), lead to a disability or permanent damage, require intervention to prevent permanent impairment or damage, or other - important medical events.), and (3) led to permanent treatment discontinuation. Both aggregate and patient level data were reviewed. The outcomes showed that the number of subjects with NPS AEs in these categories was low overall and generally similar for varenicline versus placebo, indicating that the small numerical difference in the rates of the primary NPS AE composite endpoint for varenicline versus placebo in the psychiatric cohort was not due to severe events, SAEs or events that led to permanent treatment discontinuation.

For NPS endpoint AEs that led to temporary or permanent discontinuation, the event outcomes were assessed to quantify the number of positive dechallenge outcomes, a phenomenon observed in some postmarketing cases. There was 1 positive dechallenge for varenicline observed in the non-PHx cohort compared to 4 for placebo, and 5 observed for varenicline in the PHx cohort compared to 9 for placebo. The presence of positive dechallenge outcomes in the placebo treatment group in greater numbers to those reported for varenicline, particularly in the PHx cohort, suggests that some events may be episodic in nature and/or be related to the underlying condition or the cessation attempt itself. This observation illustrates the difficulty in interpreting similar events in the postmarketing setting and suggests that the use of dechallenge outcomes in ascertainment of causality in postmarketing experience for NPS events is questionable.

Exploratory post hoc analyses of the relationship between abstinence and the onset of NPS endpoint AEs showed no clear relationship at the study or cohort level, although a potential role of abstinence cannot be ruled out for some individual subjects reporting NPS AEs.

The C-SSRS provided additional data for the evaluation of suicide-related events and showed similar percentages of subjects with suicidal ideation and/or behavior across all treatment arms within each cohort during the treatment-emergent periods. Few subjects overall reported positive responses for suicidal behavior and the single completed suicide was committed by a placebo subject in the non-PHx cohort.

Average scores from the HADS and CGI-I showed no change or slight improvement over the course of the study in both cohorts and support the conclusions from the analysis of the primary NPS AE endpoint that there is no increased risk of NPS events with varenicline.

General all-causality treatment-emergent AE data showed that within each cohort and in the study overall, similar percentages of subjects in each active treatment arm reported all-causality AEs, including SAEs and similar percentages of subjects in all treatment arms discontinued treatment due to an AE. For each active treatment, the most frequently reported AEs were consistent with the known safety profile for the drug, as reported in their respective labels.

Taken together these results show that serious NPS AEs included in the primary composite safety endpoint occur in subjects attempting to quit smoking regardless of smoking cessation treatment and show that the rates of these events are higher in subjects with a history of psychiatric disorder than those with no history of psychiatric disorder.

2.5. Efficacy

2.5.1. Evaluation of Efficacy

The primary measures of efficacy were carbon monoxide (CO)-confirmed continuous abstinence (CA) from Week 9 through Week 12 (CA 9-12) and CO-confirmed CA from Week 9 through Week 24 (CA 9-24). Smoking status was assessed by use of the NUI questionnaire, which was administered at each study visit (in-clinic visits and telephone contacts) and confirmed by CO levels measured at in-clinic visits. Subjects were considered responders (abstainers) if they answered 'no' to the questions on the NUI that asked whether the subject had smoked any cigarettes ('even a puff') since the last visit/contact and whether they had used any other nicotine-containing products including other tobacco products and NRT products (other than the study medication) for Weeks 9 through 12, and any tobacco products for Weeks 13 through 24 at each week included in the assessment period (Weeks 9-12 or 9-24)and had CO levels ≤10 ppm.

2.5.2. Statistical Methods

The efficacy analysis population was all randomized subjects.

CO-confirmed CA 9-12 (primary main efficacy analysis) and CA 9-24 (second main efficacy analysis) were evaluated using a logistic regression analysis. The statistical model included treatment arm, cohort, and region, plus the 2-way and 3-way interactions (as specified in the SAP), with possible model reduction by removal of non-significant interaction terms). The odds ratio (OR) and its associated 95% CI were estimated for all pairwise comparisons of treatment. Further, 95% CIs for the parameters CAR 9-12 and CAR 9-24 were computed for each treatment. This estimation was done both overall and by cohort via contrasts. In a conservative approach, subjects who discontinued the study were assumed to be smokers for the remainder of the study. Missing CO values were imputed as negative (ie, not disqualifying the subject as a responder). Missing NUI data were imputed using the next non-missing NUI response, if no response was available (eg, at Week 12 and Week 24) the default imputation was as a non-responder.

The main abstinence (efficacy) superiority analyses were adequately powered. Given a placebo rate of 10% and 1000 subjects per treatment arm per cohort, an OR of 2.0 could be detected at a 5% level with at least 80% power.

2.5.3. Efficacy Results

2.5.3.1. Continuous Abstinence Overall and by Cohort

A logistic regression analysis was conducted with the statistical model including terms for treatment, cohort, region (US or non-US), treatment by cohort interaction, and cohort by region. At a 10% level predetermined to identify an interaction, there was no significant interaction between treatment and cohort for either CA 9-12 or CA 9-24 (p=0.6237 and p=0.7974, respectively). Results are shown for the study overall and for each cohort separately.

Observed CAR 9-12 and CAR 9-24, overall and by cohort are shown in Table 28 and Figure 8. The ORs for each endpoint, for both the primary comparisons of varenicline vs placebo and bupropion vs placebo, as well for all other pre-specified pairwise comparisons (as secondary comparisons), are shown graphically in Figure 9.

Figure 8. CO-Confirmed Continuous Abstinence Rates, Weeks 9-12 and Weeks 9-24, Overall and by Cohort - All Randomized Subjects

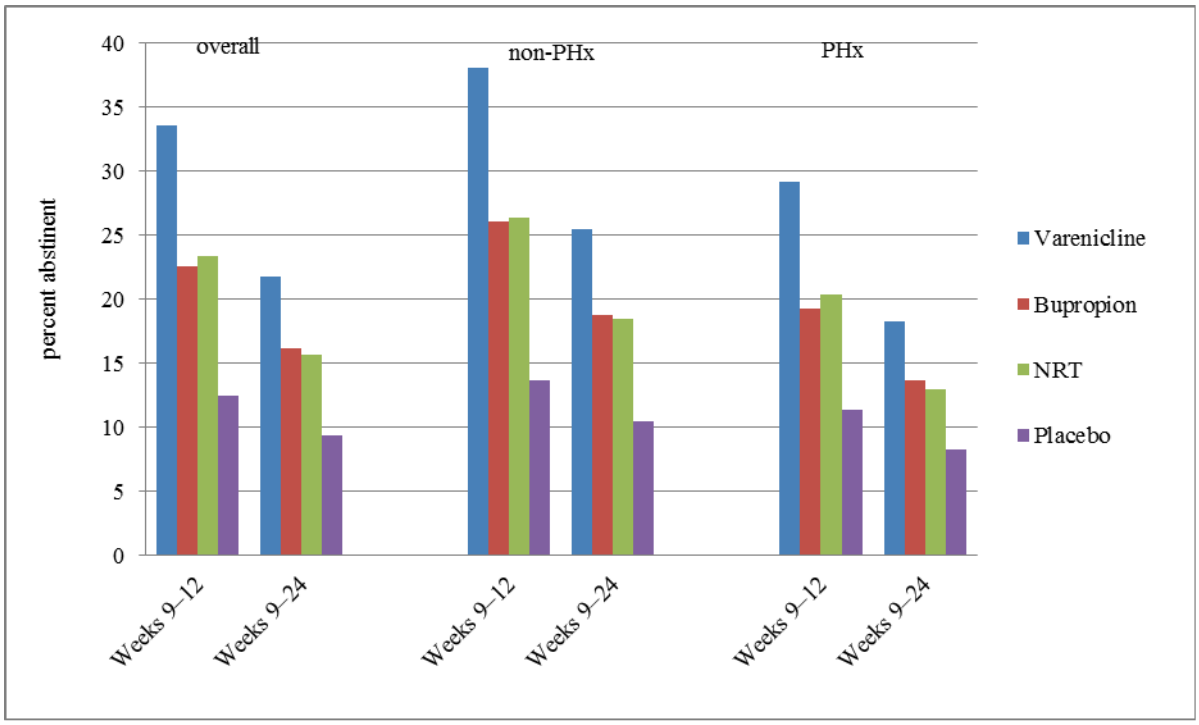


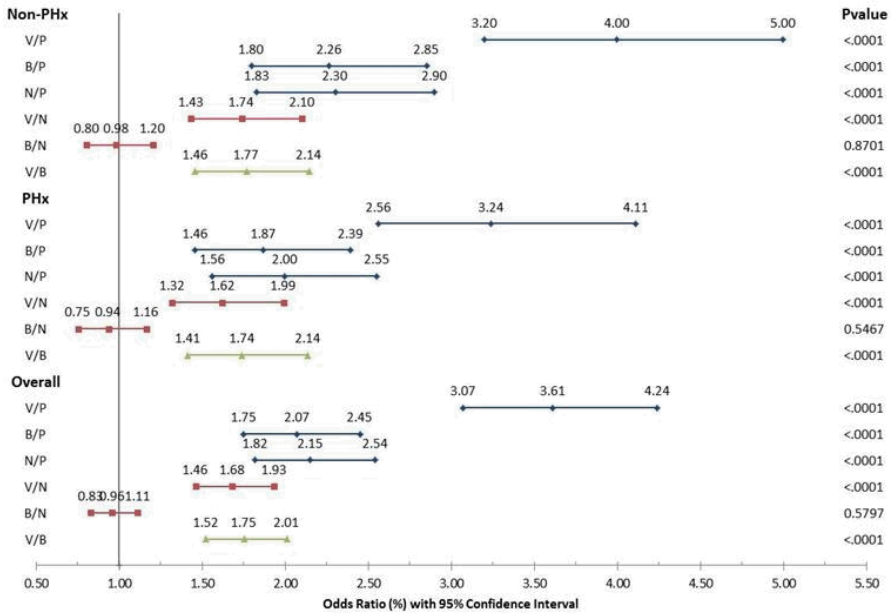
Table 28. CO-Confirmed Continuous Abstinence Rates, Weeks 9-12 and Weeks 9-24, Overall and by Cohort - All Randomized Subjects

	Overall	Non-Psychiatric History	Psychiatric History
		CAR 9-12 n/N (%)	
Varenicline	683/2037 (33.5%)	382/1005 (38.0%)	301/1032 (29.2%)
Bupropion	460/2034 (22.6%)	261/1001 (26.1%)	199/1033 (19.3%)
NRT	476/2038 (23.4%)	267/1013 (26.4%)	209/1025 (20.4%)
Placebo	255/2035 (12.5%)	138/1009 (13.7%)	117/1026 (11.4%)
		CAR 9-24 n/N (%)	
Varenicline	445/2037 (21.8%)	256/1005 (25.5%)	189/1032 (18.3%)
Bupropion	330/2034 (16.2%)	188/1001 (18.8%)	142/1033 (13.7%)
NRT	320/2038 (15.7%)	187/1013 (18.5%)	133/1025 (13.0%)
Placebo	191/2035 (9.4%)	106/1009 (10.5%)	85/1026 (8.3%)

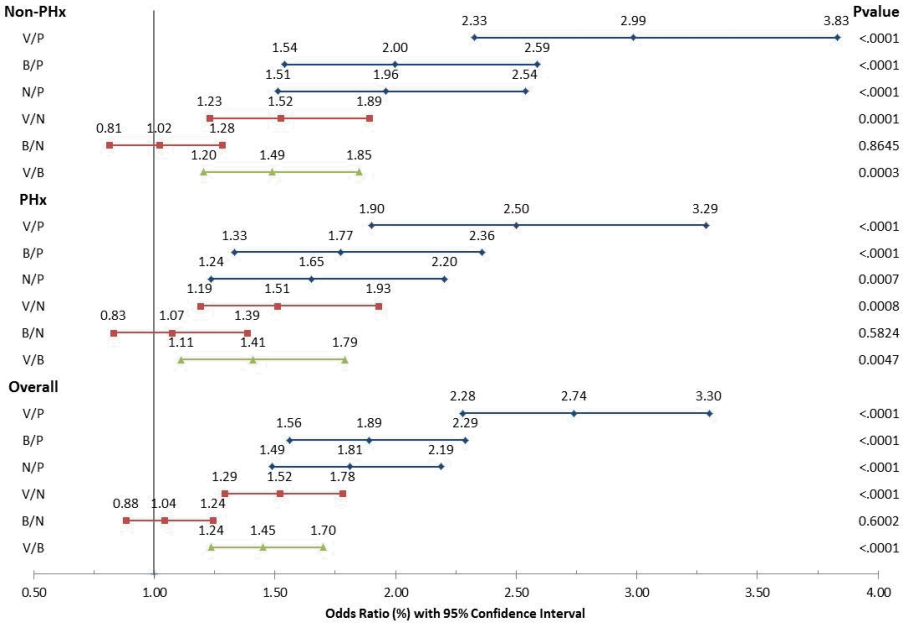
CAR=continuous abstinence rate; CO=carbon monoxide; N=number of subjects randomized to study treatment; n=number of subjects with observation of interest; NRT=nicotine replacement therapy.

Figure 9. Forest Plots of Odds Ratios for Continuous Abstinence Weeks 9-12 and Weeks 9-24, by Cohort and Overall - All Randomized Subjects

Week 9-12



Week 9-24



PHx=psychiatric history; v=varenicline; p=placebo; B=bupropion; N=nicotine replacement therapy.

For the endpoint CAR 9-12, subjects in all 3 active treatment arms had numerically higher observed abstinence rates compared to placebo, both overall and for each cohort separately, and these differences were statistically significant. Varenicline subjects had the highest observed abstinence rates, overall (33.5%) and in each cohort (38.0% non-PHx, 29.2% PHx). CARs were higher in the non-PHx cohort compared to the PHx cohort for all treatments (in the logistic regression model the effect of cohort was significant, $p<0.0001$); however, as expected based on the lack of a significant interaction between treatment and cohort, for both cohorts the ranking order of the treatments was the same: varenicline > bupropion = NRT > placebo. The OR for CAR 9-12 for the primary comparison of varenicline versus placebo was statistically significant ($p <0.0001$) overall and in each cohort, indicating that subjects treated with varenicline were more likely to quit smoking than subjects treated with placebo, regardless of cohort. The ORs for the primary comparison of bupropion versus placebo were also statistically significant, overall and in each cohort, although numerically lower than for varenicline.

The ORs for CAR 9-12 in secondary comparisons showed that varenicline subjects were more likely to quit smoking than bupropion or NRT subjects, overall and in each cohort. ORs for the secondary comparisons among the other treatments showed that NRT subjects were more likely to quit than placebo subjects and bupropion subjects were as likely to quit as NRT subjects, overall and in each cohort.

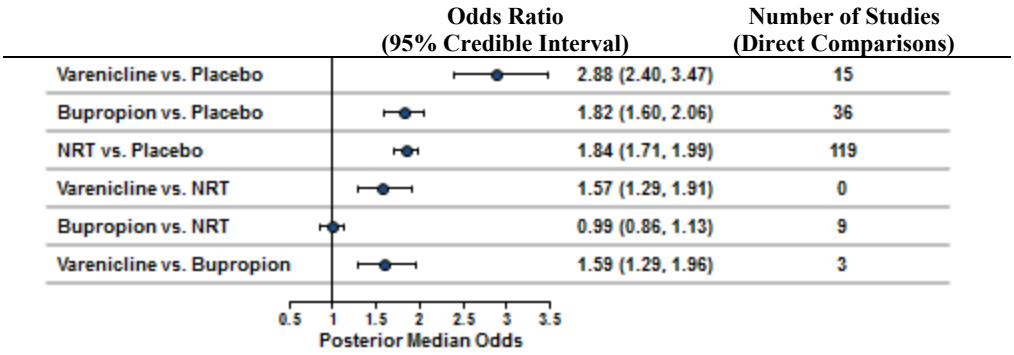
CARs for Weeks 9-24 were numerically lower than for Weeks 9-12 overall and in both cohorts for all treatment arms, but the results of the pairwise comparisons were similar for

the 2 time periods. The ranking order of the treatments was the same as CAR 9-12: varenicline>bupropion=NRT>placebo.

2.5.4. Efficacy Conclusion

EAGLES was the first direct comparison of the efficacy of the 3 FDA approved smoking cessation products currently on the market in a single, randomized, controlled, double-blind study. The results showed that all 3 active treatments, varenicline, bupropion, and NRT, had superior abstinence rates compared to placebo and that varenicline subjects had the highest abstinence rates of all treatments (ORs for CA 9-12: 3.61 [3.07, 4.24]; 2.07 [1.75, 2.45]; 2.15 [1.82, 2.54], respectively). Varenicline subjects also had superior abstinence rates compared to bupropion and NRT (ORs for CA 9-12: 1.75 [1.52, 2.01]; 1.68 [1.46, 1.93], respectively). Abstinence rates were lower in the PHx cohort than in the non-PHx cohort in all treatment arms, however, the ORs were similar between the 2 cohorts. These results corroborate the network meta-analysis done by the Cochrane group[32] prior to EAGLES to evaluate how NRT, bupropion and varenicline compare with placebo and with each other in achieving long-term abstinence (six months or longer). In that meta-analysis the results for varenicline comparisons were: varenicline vs placebo 2.88 (95% Credible Interval [Cred I] 2.40, 3.47), varenicline vs NRT 1.57 (95% Cred I 1.29, 1.91) and varenicline vs bupropion 1.59 (95% Cred I 1.29, 1.96), as shown in Figure 10.

Figure 10. Cochrane Group Network Meta-Analysis of the Comparative Efficacy of Varenicline, NRT, Bupropion, and Placebo.



Adapted from Cahill et al. [32]

3. ADDITIONAL DATA SOURCES

As noted above in Section 1.2, data from a variety of complimentary sources regarding the association of NPS events with varenicline treatment are available. Each of these data sources has inherent strengths and limitations, as noted in Table 29, but taken in totality provide a robust body of evidence. Some of these data are summarized in the sections below with additional details provided in appendices.

Table 29. Strengths and Limitations of Data Sources

Data Source	Description	Strengths Include	Limitations Include
Nonclinical studies[33]	Pharmacological profile and behavioral testing in	Allow early screening for safety signals; allow	Uncertain extrapolation to neuropsychiatric behavior in

Table 29. Strengths and Limitations of Data Sources

Data Source	Description	Strengths Include	Limitations Include
	animal models	comparison to other compounds using standardized models	humans
Postmarketing reports[34]	Collection of case reports through pharmacovigilance systems	Provide data from real world use in broader populations than those studied in clinical trials; have the potential to detect rare safety signals	Often lack medically important information; are subject to reporting biases (including stimulated reporting) and under-reporting; lack a true denominator (number of patients exposed) which limits event rate estimation; are generally not valid for making drug-drug comparisons; information required to perform an optimal scientific causality assessment can differ significantly according to the nature of the adverse event/reaction
Observational studies (Population-based) [35,36,37]	Population-based studies that collect data from large numbers of subjects with a common group identity, such as members of a health care system, residents of a state or country; may or may not involve a comparator	Provide real world data on use of a drug by actual patients; can provide reliable estimates of a safety signal; can be designed to test hypotheses about a safety signal; can complement findings from randomized trials	Possible confounding by indication (eg, due to differences in risk factors, indications for treatment or severity of illness)
Randomized, Controlled Clinical Trials (RCTs)[38]	Prospective, experimental study design specifically involving random allocation of participants to interventions.	Able to include well-defined populations with the condition of interest; randomization addresses selection bias; blinding of participants, personnel and outcome assessors (double blind RCT design) addresses the performance and detection biases.	If the population studied is defined too narrowly, the ability to generalize the data to real world populations is limited; studies could have insufficient power to detect an effect of the intervention; patients with AEs may drop out resulting in attrition bias.
Meta-analyses of RCTs[38]	Statistical analyses of combined data from multiple RCTs	Provide an increase in power, diversity of trials, confer an improvement in precision, the ability to answer questions not resolved by individual studies, and allows for testing of the robustness of outcomes through sensitivity analyses.	May provide incorrect outcomes, particularly if specific study designs, within-study biases, variation across studies, and reporting biases are not addressed.

RCT=randomized, controlled trial.

3.1. Biological Plausibility of Serious NPS Adverse Events

Clinical data from controlled trials, meta-analyses, observational cohort studies and the EAGLES safety trial are key to assess whether varenicline use is causally related to the serious NPS AEs that are being evaluated. It is important, however, to also consider the biological plausibility, taking into account varenicline's mechanism of action and nonclinical profile, in determining causality for this type of AE.

In vitro studies demonstrate that varenicline has high selectivity for α4β2 and α6β2-containing (α6β2*) subtypes of nAChRs and does not bind to targets that have been implicated in CNS disorders, and thereby associated with serious NPS AEs. The results of in vivo studies demonstrate that while both varenicline and nicotine moderately stimulate dopamine release, neither depletes nor produces large increases in neurotransmitters. At pharmacologically relevant exposures, varenicline does not cause adverse behavioral CNS effects or neurological signs in animals, based upon safety pharmacology or chronic toxicity studies conducted during development. Furthermore, varenicline does not impair behavior in several animal tests that assess effects on mood, sensory gating and cognitive processing. The combined results of nonclinical studies have not identified a pharmacological mechanism to explain the observed reports of serious NPS AEs.

Importantly, data also indicate that varenicline's nonclinical profile is comparable to that of nicotine used in NRT, which has not been associated with a risk of serious NPS AEs. Details of these data can be found in Appendix 2.

3.2. Published Clinical Studies

3.2.1. Additional Pfizer Sponsored Randomized Control Trial

An additional Pfizer sponsored placebo-controlled trial was completed and published after data from 2 meta-analyses of Pfizer studies were included in CHANTIX labeling (see Section 1.2). In the **Ebbert et al**[39] study, smokers who were not willing or able to quit within the next month but who were willing to reduce smoking and make a quit attempt within the next 3 months, were randomized to varenicline (n=760) or placebo (n=750) for 24 weeks of treatment. NPS AEs that occurred in ≥2% of subjects in either treatment arm were anxiety (6.9% for varenicline vs 8.8% for placebo), irritability (5.2% vs 4.0%), depressed mood (3.5% vs 3.6%), depression (3.3% vs 4.7%) and agitation (2.7 vs 1.9%). Results of the C-SSRS for the treatment period and up to 30 days after last dose showed that suicidal ideation or behavior was recorded in 0.8% of varenicline and 1.3% of placebo subjects. Any increases in Patient Health Questionnaire (PHQ)-9 depression scores from baseline to any time point after baseline occurred in 22.5% of varenicline and 19.5% of placebo treated subjects (P=.16). The authors stated "varenicline did not increase the risk of suicidal ideation or behavior or other psychiatric adverse events."

3.2.2. Literature Review of Non-Pfizer Randomized, Controlled Clinical Trials Reporting NPS Events

An update to the literature search included in the Pfizer 2014 FDA Advisory Committee Briefing Document[40] was performed (see Appendix 3 for the literature search results included in the 2014 FDA Advisory Committee Briefing Document). The objective of the

search was to identify additional double–blind, randomized, controlled trials (RCT) or meta-analyses (or other combined/pooled analyses) of randomized, controlled trials that reported NPS safety results for varenicline vs placebo or another comparator. The following databases were searched (using a date range of 25 February 2014 through 23 May 2016) for varenicline and various NPS keywords and mental disorders subject headings: Ovid Medline, Embase, Embase Daily Alerts and Derwent Drug File. The search terms were based on NPS terms that are included in the US CHANTIX label and included: psychiatric, neuropsychiatric, mental disorders, suicide, suicidal ideation, suicidal behavior, suicide attempt, self-harm, depression, depressive disorder, depressed mood, mood disorder, schizophrenia, hallucination, delusion, psychosis, paranoia, mania, manic disorder, bipolar disorder, anxiety, panic, agitation, aggression, aggressive behavior, hostility, hostile behavior, abnormal behavior, changes in behavior or thinking, and personality disorder.

Preclinical publications, conference literature, and other publication types such as notes, comments, editorials and non-English language publications were excluded during the search process. Studies in non-smokers, populations using varenicline for indications other than smoking cessation, studies in which all patients received varenicline, crossover or methodology studies, studies of less than 20 subjects treated with varenicline, and publications not reporting original data or new analysis (such as review articles) or not reporting any NPS results were excluded during the review of the search results.

The review of the literature identified 13 relevant publications matching the search objective. Of these, 6 publications included results from meta-analyses and other combined analyses and 7 were individual clinical trial publications. Only NPS results for these publications are summarized.

3.2.3. Meta-Analyses and Other Pooled/Combined Analyses of Randomized Controlled Trials

The 6 meta-analyses or other combined/pooled analyses found no evidence of increased NPS risk with varenicline when compared with placebo. The analyses are summarized in Table 30 below and additional details are provided in Appendix 3.

Table 30. Summary of 6 Meta-Analyses and Other Pooled/Combined Analyses of Randomized Controlled Trials

Lead Author	Number of Studies and Study Population	Comparator	Varenicline NPS Findings
1) Thomas[41]	39 RCTs of 5817 varenicline and 4944 placebo treated subjects	Placebo	No evidence of an increased risk of suicide or attempted suicide, suicidal ideation, depression, irritability, aggression, anxiety, or death with varenicline
2) Foulds[42]	8 RCTs of 2403 varenicline and 1434 placebo treated subjects without current psychiatric disorder	Placebo	Varenicline does not increase NPS symptoms such as depressed mood and irritability measured on the MNWS in smokers without current psychiatric disorders

Table 30. Summary of 6 Meta-Analyses and Other Pooled/Combined Analyses of Randomized Controlled Trials

Lead Author	Number of Studies and Study Population	Comparator	Varenicline NPS Findings
3) Avery[43]	2 studies one with 152 postmenopausal women treated with placebo(95 subjects) or nicotine patch (57 subjects) and the other with 78 women treated with varenicline	Placebo or NRT patch	Subjects taking varenicline had lower rates of depressive symptoms over all time points compared with those taking NRT or placebo
4) Kishi[44]	7 RCTs (6 in subjects with schizophrenia and 1 in subjects with schizophrenia and bipolar) of 237 varenicline and 202 placebo treated subjects	Placebo	No significant difference detected in suicidal ideation and depression between varenicline and placebo
5) Wu[45]	8 RCTs in subjects with severe mental illness; 158 varenicline and 114 placebo treated subjects	Placebo	No significant difference seen between varenicline and placebo in terms of suicidal ideation, depressed mood, anxiety, and mood swings
6) Cahill[46]	39 RCTs of 11,801 varenicline and 7109 placebo, 2935 bupropion or 3445 NRT patch treated subjects	Placebo, bupropion or NRT patch	No evidence of an increased risk of depression, suicidal ideation, or serious neuropsychiatric AEs. Authors conclude that "early reports of possible links to suicidal ideation and behavior have not been confirmed by current research".

RCT=randomized, controlled trial; NPS=neuropsychiatric; MNWS=Minnesota Nicotine Withdrawal Scale; NRT=nicotine replacement therapy..

3.2.4. Randomized Controlled Clinical Trials

Of the 7 clinical trial publications, 3 publications did not recruit subjects with a specific psychiatric comorbidity. Of those 3, 2 publications (1-2) involved comparisons of varenicline to placebo and 1 had an active comparator (3). The last 4 publications summarized (4-7) were based on RCTs conducted in patients with a psychiatric history. The studies are summarized in Table 31 below and details are provided in Appendix 3.

Table 31. Summary of 7 Randomized, Controlled Clinical Trials

Lead Author	Study Design and Population	Intervention	Varenicline NPS Findings
1) Nahvi[47]	Double-blinded; smokers enrolled in methadone maintenance treatment program	112 subjects randomized to varenicline (n=57) or placebo (n=55) for 12 weeks of treatment	The incidence of major depressive, manic episodes, or psychotic disorders was infrequent, and did not differ between treatment arms. There was no difference in odds of suicidal ideation between treatment arms. There was no observed association between varenicline and adverse psychiatric effects.
2) Eisenberg[48]	Double-blind; hospitalized smokers with an	302 subjects randomized to varenicline (n=151) or	No cases of suicidal ideation in the study. A single NPS event involving hospitalization for depression occurred in a patient 25 days

Table 31. Summary of 7 Randomized, Controlled Clinical Trials

Lead Author	Study Design and Population	Intervention	Varenicline NPS Findings
	ACS	placebo (n=151) for 12 weeks	after taking one dose of varenicline. Similar numbers of patients in each treatment arm discontinued treatment within 30 days because of AEs.
3) Lerman[49]	Double-blind study evaluating a nicotine metabolite ratio (NMR) in smokers	1246 subjects randomized to varenicline (n=420), NRT patch (n=418), or placebo (n=408) for 11 weeks	In normal metabolizers, varenicline led to decreases in irritability, anxiety, and attentional disturbance.
4) Chengappa[50]	Double-blind; smokers with DSM-IV bipolar disorder.	60 subjects randomized to varenicline (n=31) and placebo (n=29) for 12 weeks	There was no significant difference among treatment-emergent AEs between treatments, including C-SRRS items for suicidality. Psychopathology scores remained stable throughout the study period regardless of treatment assignment. Depressed mood trended higher in varenicline vs placebo but not significant (Fisher exact test, P= .08). Authors concluded that "vigilance for NPS adverse events is prudent when initiating varenicline for SC in this patient population."
5) Shim[51]	Double blind; smokers and non-smokers with schizophrenia	120 subjects randomized to varenicline (n=60) or placebo (n=60) for up to 8 weeks	The study utilized several scales for which results showed no significant main effects of treatment or time by treatment arm interactions in the PANSS and SANS or CGI severity. No subject in either group had increases in depressive symptoms measured by HAM-D.
6) Tulloch[52]	Open-label; smokers with and without a psychiatric history	737 subjects randomized to standard NRT patch (for 10 weeks; n=245), extended use of combination NRT (patch plus gum or inhaler for up to 22 weeks; n=245) or varenicline (for up to 24 weeks; n=247)	59% of subjects in this study had a lifetime psychiatric diagnosis. There were no significant differences in NPS AEs (such as anxiety, concentration and suicidal ideation) among treatment arms or between the psychiatric and non-psychiatric cohort.
7) Smith[53]	Double-blind; smokers with DSM-IV diagnosis of schizophrenia or schizoaffective disorder	87 subjects randomized to varenicline (n=42) or placebo (n=45) for 8 weeks	Varenicline subjects did not show any worsening of psychopathology scores, including positive symptoms and depression. No increase was found in any component of psychiatric symptoms with varenicline. No subject reported a clear increase of suicidal ideation and no suicides or new emergency acute depressive episodes

Table 31. Summary of 7 Randomized, Controlled Clinical Trials

Lead Author	Study Design and Population	Intervention	Varenicline NPS Findings
			occurred.

AEs=adverse events; C-SSRS=Columbia Suicide Severity Rating Scale; NPS=neurpsychiatric; SC=smoking cessation; PANSS=Positive and Negative Syndrome Scale; SANS=Scale for the Assessment of Negative Symptoms; CGI=Clinical Global Impression; HAM-D=Hamilton Depression Rating Scale.; NRT=nicotine replacement therapy; DSM-IV= Diagnostic and Statistical Manual of Mental Disorders 4th Edition.

3.2.5. Conclusions of Published Clinical Trials

Since the time of Pfizer's 2014 Advisory Committee Briefing Document, an updated review of the literature has identified an additional 6 meta-analyses and 8 randomized controlled trials, including 1 trial conducted by Pfizer, that reported on NPS safety for varenicline when used in smokers. A review of these studies suggests that varenicline is not associated with an increased risk of serious NPS AEs.

3.3. Published Observational Studies Not Sponsored by Pfizer

Observational (population-based) studies can complement findings from randomized trials. They provide real world data on use of a drug by actual patients and can be designed to test hypotheses about a specific safety signal. Because they are typically of large size, such studies can provide reliable estimates of safety signals.

3.3.1. Observational Studies Included in the Current CHANTIX Label

As noted in Section 1.2, the CHANTIX label[4] currently contains information from 4 observational cohort studies of selected serious NPS AEs. Tabular summaries of these studies are provided in Appendix 4.

These 4 observational studies provide no evidence that varenicline users were more likely to inflict fatal or non-fatal self-harm, to initiate pharmacological treatment for depression or to be hospitalized for an NPS condition relative to users of NRT.[54,55,56] Relative to bupropion users, varenicline users were no more likely to be treated at an emergency department or be hospitalized for a neuropsychiatric condition.[57]

3.3.2. Subsequent Observational Studies

To identify additional population-based observational studies that became available after the 4 observational studies already described in the Chantix USPI, Pfizer conducted a literature search that used the same NPS safety terms described in Section 3.2. The search identified 4 additional relevant publications, 1 of which (Cunningham et al, 2016)[58] appears to be the unpublished study by the Department of Veteran Affairs that is described in the CHANTIX label. One of the 4 studies was not included in this review because of its small size (125 varenicline treatment episodes) and cross-sectional design.[59] The remaining 3 studies are summarized below.

Design aspects of all 3 studies are summarized in Table 32 below.

Table 32. Summary of Three Subsequent Population-Based Observational Cohort Studies

Lead Author	Source Population	Study Period	Comparator	Primary Endpoint(s)
Molero[60]	Population of Sweden	22Nov06 to 31Dec09	Non treatment period; subject serves as own control	Hospital admission or unplanned outpatient specialist visit for incident psychosis or mood or anxiety condition; Emergency inpatient or outpatient hospital visit or death due to intentional self-harm
Kotz[61]	UK general practice	01Jan07 to 30Jun12	NRT	Incident occurrence within 6 months of treatment initiation of: a) depression; and b) fatal or non-fatal intentional self-harm
Cunningham[58]	US Veterans Health Administration	01May06 to 30Sep07	Nicotine patch	Primary inpatient discharge diagnosis for 7 separate psychiatric conditions within 30 days of treatment initiation

NRT=nicotine replacement therapy; UK=United Kingdom; US=United States.

The results of these 3 studies are summarized in Table 33 below and additional details are provided in Appendix 4.

Table 33. Summary of Primary Results from Three Subsequent Population-Based Observational Cohort Studies with Comparators

Endpoint	Author	Varenicline # Events/ Sample Size	Comparator # Events/ Sample Size	Hazard Ratio	95% CI	
					Lower Limit	Upper Limit
Fatal or non-fatal self-harm	Kotz	119 / 51,450	540 / 106,759	0.56	0.46	0.68
	Molero	657 / 69,757	NA	1.00	0.72	1.37
Incident psychiatric condition	Molero	3,213 / 69,757	NA	1.18	1.05	1.31
Incident depression	Kotz	2,395 / 51,450	8,274 / 106,759	0.66	0.63	0.69
Primary inpatient discharge diagnosis within 30 days of treatment initiation for:						
Depression	Cunningham	6 / 11,774	12 / 23,548	1.00	0.38	2.67
Bipolar disorder	Cunningham	1 / 11,774	13 / 23,548	0.15	0.02	1.18
Schizophrenia	Cunningham	3 / 11,774	12 / 23,548	0.50	0.15	1.62
Other psychosis	Cunningham	4 / 11,774	12 / 23,548	0.67	0.22	2.07

Table 33. Summary of Primary Results from Three Subsequent Population-Based Observational Cohort Studies with Comparators

Endpoint	Author	Varenicline # Events/ Sample Size	Comparator # Events/ Sample Size	Hazard Ratio	95% CI	
					Lower Limit	Upper Limit
PTSD	Cunningham	2 / 11,774	9 / 23,548	0.44	0.10	2.06
Drug-induced disorder	Cunningham	4 / 11,774	4 / 23,548	2.00	0.50	8.00
Suicide attempt	Cunningham	0 / 11,774	0 / 23,548	NA	NA	NA

One study examined seven mental health disorders and found no evidence of an increased risk for hospitalization for any of them when comparing varenicline users compared to nicotine patch users.[58] The study also examined out-patient clinic visits for the same disorders as secondary endpoints (not shown in Table 33) and found no evidence of an increased risk for any disorder except schizophrenia (HR=1.27; 95%CI:1.07-1.51). A second study[61] found varenicline users were less likely than NRT users to experience incident depression (HR=0.66; 95%CI:0.63-0.69) and self-harm (HR=0.56; 95%CI:0.46-0.68). The third study[60] found an increased risk of incident psychiatric conditions during varenicline treatment compared to periods of non-treatment within the same person (HR=1.18; 95%CI:1.05-1.31). Further analysis isolated the effect to an increased risk of incident anxiety conditions (HR=1.23; 95%CI:1.01-1.51) and mood conditions (HR=1.31; 95%CI:1.06-1.63) among people with pre-existing psychiatric disorders and found no evidence of increased risk among those with no pre-existing disorders.

3.3.3. Observational Studies Conclusions

The 4 population-based observational cohort studies described in the CHANTIX USPI provide no evidence that varenicline users were more likely to inflict fatal or non-fatal self-harm, to initiate pharmacological treatment for depression or to be hospitalized for a neuropsychiatric condition relative to users of NRT. Relative to bupropion users, varenicline users were no more likely to be treated at an emergency department or be hospitalized for a neuropsychiatric condition.

Pfizer conducted a literature search that identified 4 additional population-based observational cohort studies that were published after the 4 observational studies already described in the CHANTIX labeling. One of the studies[58] appears to be the unpublished study by the Department of Veteran Affairs that is described in the Chantix USPI. One of the 4 studies was not included in this review because of its small size (125 varenicline treatment episodes) and cross-sectional design.[59]

The primary analyses of the primary endpoints of 2 studies found no evidence of an increased risk for a wide variety of incident serious neuropsychiatric events in patients treated with varenicline compared to NRT[61] or nicotine patch[58]. An increased risk for a secondary endpoint, out-patient clinic visits for schizophrenia, was found for varenicline

users compared to nicotine patch users.[58] A third study[60] found an increased risk of incident anxiety and mood conditions during varenicline treatment compared to periods of non-treatment within the same person, but only among people with pre-existing psychiatric disorders.

These real-world data were gathered among a broader selection of patients, including patients with psychiatric disorders, and thereby generalize the clinical trials results to the overall population of smokers. Other strengths of these studies include their relatively large drug cohort sizes, the use of self-controlled designs or propensity scores to minimize the effects of potential confounders. Like all observational studies, the lack of randomization in these studies leaves the potential for selection bias and, despite attempts to control confounding, there is always the possibility of residual confounding.

4. OVERALL CONCLUSIONS AND PROPOSED LABEL CHANGES

EAGLES represents the largest prospectively designed, randomized, controlled study to evaluate the risk of serious NPS AEs in subjects using varenicline, bupropion and NRT as smoking cessation therapies and includes the largest cohort of subjects with a history of a psychiatric disorders in a randomized, controlled study to date. Elements of the study design address the limitations inherent in the postmarketing data that first identified the signal for NPS AEs, such as potential reporting bias, lack of a standardized endpoint, the inability to establish incidence rates, and lack of a control group. Other features of the study addressed concerns about the ability of a clinical study to robustly capture the types of serious NPS AEs reported in the postmarketing experience.

The outcomes of EAGLES showed that serious NPS AEs included in the primary composite safety endpoint occur in subjects attempting to quit smoking regardless of smoking cessation treatment and showed that the rates of these events are higher in subjects with a history of psychiatric disorder than those with no history of psychiatric disorder.

The study outcomes showed no significant increase in the incidence of serious NPS AEs included in the primary composite safety endpoint in subjects treated with varenicline compared to subjects treated with placebo or NRT patch (over-the-counter [OTC] smoking cessation medication), in subjects with or without a history of psychiatric disorder. In the non-psychiatric cohort, the incidence of NPS events in the composite endpoint was low overall and there was a small numerical decrease for varenicline compared to placebo. In the psychiatric cohort, a small numerical increase in the incidence of the composite endpoint in varenicline versus placebo was observed but was not driven by events that were serious or severe in nature or that led to treatment discontinuation.

The efficacy outcomes of EAGLES confirmed varenicline as the most effective monotherapy treatment option currently available for smokers who want to quit and thus reaffirm the importance of the use of varenicline as an aid to smoking cessation treatment in combating the public health crisis caused by cigarette smoking.

Timely communication of the newly acquired data is important and product labeling should accurately reflect the product safety and efficacy profile in order for patients and prescribers to make informed decisions about treatment. Based on the totality of scientific evidence

available to date, including the safety and efficacy outcomes of EAGLES, Pfizer believes that the boxed warning regarding reports of serious NPS adverse events in patients attempting to quit smoking with CHANTIX as currently included in the CHANTIX label, does not accurately reflect the NPS safety profile of CHANTIX and should be removed as it has the potential to deter appropriate use of CHANTIX.

Nevertheless, given that serious NPS AEs have been reported in the postmarketing experience in patients attempting to quit smoking with CHANTIX, and acknowledging that controlled clinical trials may not be able to completely rule out very rare or idiosyncratic events, Pfizer proposes to retain the WARNINGS and PRECAUTIONS section of the label regarding NPS events occurring in patients attempting to quit smoking and also include the information regarding NPS events from the EAGLES trial in this section. Pfizer believes that such warning sufficiently alerts prescribers to the possibility that these types of events may occur in smokers attempting to quit.

The specific label changes proposed are shown below:

- *Highlights of Prescribing Information:*
  - Remove Boxed Warning on Serious Neuropsychiatric Events
  - Under Warnings and Precautions, add information on Serious Neuropsychiatric Symptoms

- *BOXED WARNING section of the Full Prescribing Information (FPI):*
  - Remove the boxed warning on Serious Neuropsychiatric Events

- *WARNINGS AND PRECAUTIONS section of the FPI:*
  - Revise information in section 5.1 WARNINGS AND PRECAUTIONS/Neuropsychiatric Symptoms and Suicidality and add safety outcomes from the Study in Patients with or without a History of Psychiatric Disorder (EAGLES)

- *ADVERSE REACTIONS section of the FPI:*
  - In section 6.1 ADVERSE REACTIONS/Clinical Trials Experience, add information regarding common adverse events reported in the Study of Patients with or without a History of Psychiatric Disorder (EAGLES)

- *CLINICAL TRIALS section of the FPI:*
  - Add new subsection 14.6 entitled, “Subjects with or without a History of Psychiatric Disorder”, containing efficacy information from the EAGLES study

- *PATIENT COUNSELING INFORMATION section of the FPI:*
  - Revise Section 17 PATIENT COUNSELING INFORMATION/Neuropsychiatric Symptoms

Corresponding revisions were also proposed to the Chantix patient Medication Guide.

REFERENCES

[3] CHANTIX [US Package Insert]. New York, NY: Pfizer Inc; 2009.

[4] CHANTIX [US Package Insert]. New York, NY: Pfizer Inc; 2014.

[5] Department Health and Human Services. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014. http://www.surgeongeneral.gov/library/reports/50-years-of-progress/full-report.pdf [accessed 30 June 2016].

[6] Centers for Disease Control and Prevention Fact Sheet – Health Effects of Smoking. http://www.cdc.gov/tobacco/data_statistics/fact_sheets/health_effects/effects_cig_smoking/index.htm [accessed 30 June 2016]

[7] Carter BD, Abnet CC, Feskanich D, et al. Smoking and mortality—beyond established causes. N Engl J Med 2015;372(7):631-40.

[8] Centers for Disease Control and Prevention Fact Sheet – Quitting Smoking. http://www.cdc.gov/tobacco/data_statistics/fact_sheets/cessation/quitting [accessed 1 August 2016].

[9] Clarke TC, Ward BW, Freeman G, et al. Early release of selected estimates based on data from the January-March 2015 National Health Interview Survey. In: Atlanta, GA: National Center for Health Statistics, 2015:116 pages.

[10] Centers for Disease Control and Prevention. Current Cigarette Smoking Among Adults—United States, 2005–2012. Morbidity and Mortality Weekly Report 2014;63(02):29–34 https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6302a2.htm [accessed 30 June 2016]

[11] Centers for Disease Control and Prevention. Smoking among U.S. adults with mental illness 70 percent higher than for adults with no mental illness http://www.cdc.gov/media/releases/2013/p0205_smoking_mentally_ill.html [accessed 7 July 2016]

[12] Centers for Disease Control and Prevention. Vital Signs: Current Cigarette Smoking Among Adults Aged ≥18 Years with Mental Illness — United States, 2009–2011. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6205a2.htm?s_cid=mm6205a2_w

[13] Centers for Disease Control and Prevention. Current Cigarette Smoking Among U.S. Adults Aged 18 Years and Older. http://www.cdc.gov/tobacco/campaign/tips/resources/data/cigarette-smoking-in-united-states.html

[14] Lawrence D, Williams JM. Trends in smoking rates by level of psychological distress-time series analysis of US National Health Interview data 1997-2014. Nicotine Tob Res 2016;18(6):1463-70.

[15] US Department of Health and Human Services. Ending the Tobacco Epidemic: a tobacco control strategic action pPlan for the U.S. Department of Health and Human Services. In: Washington, DC: Office of the Assistant Secretary for Health, Nov 2010:62 pages.

[16] Glassman AH, Hetzer JE, Covey LS, et al. Smoking, smoking cessation, and major depression. JAMA 1990;264(12):1546-9.

[17] Ziedonis D, Hittsman B, Beckham C, et al. Tobacco use and cessation in psychiatric disorders: National Institute of Mental Health report. Nicotine Tob Res 2008;10(12):1691-715.

[18] Schroeder SA, Morris CD. Confronting a neglected epidemic: tobacco cessation for persons with mental illnesses and substance abuse problems. Annu Rev Public Health 2010;31:297–314.

[19] American Legacy Foundation. A hidden epidemic: tobacco use and mental illness. Washington, DC: American Legacy Foundation, 2011. https://smokingcessationleadership.ucsf.edu/sites/smokingcessationleadership.ucsf.edu/files/Documents/FactSheets/a_hidden_epidemic_legacy_june_2011.pdf

[20] Torres LD, Barrera AZ, Delucchi K, et al. Quitting smoking does not increase the risk of major depressive episodes among users of Internet smoking cessation interventions. Psychol Med 2010;40(3):441-9.

[21] Tsoh JY, Humfleet GL, Munoz RF et al. Development of major depression after treatment for smoking cessation. Am J Psychiatry 2000;157:368-74.

[22] Kahler CW, Brown RA, Ramsey SE et al. Negative mood, depressive symptoms, and major depression after smoking cessation treatment in smokers with a history of major depressive disorder. J Abnorm Psychol 2002;111(4):670-5.

[23] Hall SM, Prochaska JJ. Treatment of smokers with co-occurring disorders: emphasis on integration in mental health and addiction treatment settings. Annu Rev Clin Psychol 2009;5:409-31.

[24] Thorndike AN, Stafford RS, Rigotti NA. US physicians' treatment of smoking in outpatients with psychiatric diagnoses. Nicotine Tob Res 2001;3(1):85-91.

[25] Prochaska, JJ, Reyes, RS, Schroeder, SA, et al. An online survey of tobacco use, intentions to quit, and cessation strategies among people living with bipolar disorder. Bipolar Disord 2011;13:466–73.

[26] Prochaska JJ, Gill P, Hall, SM. Treatment of tobacco use in an inpatient psychiatric setting. Psychiatr Serv 2004;55(11):1265-70.

[27] Taylor G, McNeill A, Girling A. Change in mental health after smoking cessation: systematic review and meta-analysis BMJ 2014;348:g1151.

[28] Baker A, Richmond R, Haile M, et al. A randomized controlled trial of a smoking cessation intervention among people with a psychotic disorder. Am J Psychiatry 2006;163(11):1934-42.

[29] FDA Briefing Document Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee, October 16, 2014, Chantix and Serious Neuropsychiatric Adverse Events. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM418705.pdf

[30] Coyne K, Margolis MK. 2011. Assessing the Content Validity of the Neuropsychiatric Adverse Events Interview (NAEI). A10187. Available on request.

[31] FDA. What is a serious adverse event? http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm, [accessed 26 June 2016]

[32] Cahill K, Stevens S, Perera R, et al. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst Rev 2013, 5:CD009329.

[33] Nestler EJ, Hyman SE. Animal models of neuropsychiatric disorders. Nature Neuroscience 2010;13:1161–9.

[34] CDER. The Clinical Impact of Adverse Event Reporting. MedWatch Continuing Education Article. October 1996. http://www.fda.gov/downloads/safety/medwatch/ucm168505.pdf

[35] Szklo M. Population–based cohort studies. Epidemiologic Rev 1998;20:81-90.

[36] Silverman SL. From randomized controlled trials to observational studies. Am J Med 2009; 122:114-20.

[37] Booth CM, Tannock IF. Randomised controlled trials and population-based observational research: partners in the evolution of medical evidence. Br J Cancer 2014; 110:551-5.

[38] Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration. Version 5.1.0. [updated March 2011] Editors: Julian PT Higgins and Sally Green http://www.cochrane.org/handbook#formats [accessed 1 Aug 2016]

[39] Ebbert J, Hughes J, West R et al. Effect of varenicline on smoking cessation through smoking reduction: A randomized clinical trial. JAMA. 2015;313(7):687-94.

[40] Pfizer Briefing Document Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee, October 16, 2014. Risk of Serious Neuropsychiatric Adverse Events with CHANTIX (varenicline tartrate). http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM418706.pdf

[41] Thomas KH, Martin RM, Knipe DW et al. Risk of neuropsychiatric adverse events associated with varenicline: systematic review and meta-analysis. BMJ 2015;350:h1109 doi10.1136/bmj.h1109.

[42] Foulds J, Russ C, Yu CR, et al. Effect of Varenicline on Individual Nicotine Withdrawal Symptoms: A Combined Analysis of Eight Randomized, Placebo-Controlled Trials. Nicotine Tob Res. 2013 Nov;15(11):1849-57. doi: 10.1093/ntr/ntt066

[43] Avery N, Kenny AM, Kleppinger A, Brindisi J, Litt MD, Oncken CA. Effects of varenicline, nicotine or placebo on depressive symptoms in postmenopausal smokers. Am J Addict. 2014 Sep-Oct;23(5):459-65. doi: 10.1111/j.1521-0391.2014.12130.x.

[44] Kishi T, Iwata N. Varenicline for Smoking Cessation in People with Schizophenia: Systematic Review and Meta-Analysis. Eur Arch Psychiatry Clin Neurosci 2016; 265:259-68.

[45] Wu Q, Gilbody S, Peckham E, et al. Varenicline for smoking cessation and reduction in people with severe mental illnesses: systematic review and meta-analysis. Addiction 2016 ;Apr 4.

[46] Cahill K, Lindson-Hawley N, Thomas KH, et al. Nicotine receptor partial agonists for smoking cessation. Cochrane Database of Systematic Reviews. 2016 May 9;(5):CD006103.

[47] Nahvi S, Ning Y, Segal KS, et al. Varenicline efficacy and safety among methadone maintained smokers: A randomized placebo-controlled trial. Addiction. 2014 Sep;109(9):1554-63. doi: 10.1111/add.12631.

[48] Eisenberg MJ, Windle SB, Roy N et al. Varenicline for smoking cessation in hospitalized patients with acute coronary syndrome. Circulation. 2016 Jan 05;133(1):21-30.

[49] Lerman C, Schnoll RA, Hawk LW, et al. . Use of the nicotine metabolite ratio as a genetically informed biomarker of response to nicotine patch or varenicline for smoking cessation: a randomised, double-blind placebo-controlled trial. Lancet Respir Med. 2015 Jan 11. doi: 10.1016/S2213-2600(14)70294-2

[50] Chengappa KNR, Perkins KA, Brar JS, et al. Varenicline for Smoking Cessation in Bipolar Disorder: A Randomized, Double-Blind, Placebo-Controlled Study. J Clin Psychiatry. 2014;75(7):765-72. doi: 10.4088/JCP.13m08756

[51] Shim JC, Jung DU, Jung SS, Seo YS, Cho DM, Lee JH, Lee SW, Kong BG, Kang JW, Oh MK, Kim SD, McMahon RP, Kelly DL. Adjunctive varenicline treatment with antipsychotic medications for cognitive impairments in people with schizophrenia: a randomized double-blind placebo-controlled trial. Neuropsychopharmacology. 2012 Feb;37(3):660-8.

[52] Tulloch HE, Pipe AL, Els C, et al. Flexible, dual-form nicotine replacement therapy or varenicline in comparison with nicotine patch for smoking cessation: a randomized controlled trial. BMC Med. 2016 Jun 7;14(1):80. doi: 10.1186/s12916-016-0626-2.

[53] Smith RC, Amiaz R, Si T-M, et al. Varenicline effects on smoking, cognition, and psychiatric symptoms in schizophrenia: A double-blind randomized trial. PLoS ONE. 2016 Jan 05;11 (1):e0143490.

[54] Thomas KH, Martin RM, Davies NM, et al. Smoking cessation treatment and risk of depression, suicide, and self harm in the Clinical Practice Research Datalink: prospective cohort study. BMJ 2013;347:f5704.

[55] Meyer, TE, Taylor, LG, Xie, S, et al. Neuropsychiatric events in varenicline and nicotine replacement patch users in the Military Health System. Addiction, 2013; 108:203–10. doi: 10.1111/j.1360-0443.2012.04024.x

[56] US Department of Veterans Affairs
http://www.fda.gov/Drugs/DrugSafety/ucm276737.htm#s

[57] Pasternak B, Svanström H, Hviid A. Use of varenicline versus bupropion and risk of psychiatric adverse events. Addiction 2013;108: 1336–43. doi: 10.1111/add.12165

[58] Cunningham FE, Hur K, Dong D, et al. A comparison of neuropsychiatric adverse events during early treatment with varenicline or a nicotine patch. Addiction 2016; 111(7):1283–92.

[59] Shewale AR, Borse MS, Brown JD, et al. Mental health status of varenicline and bupropion users during a quit attempt compared to current smokers, other quitters, and non-smokers. Drug Alcohol Depend 2015;154:132-8.

[60] Molero Y, Lichtenstein P, Zetterquist J, Gumpert CH, Fazel S. Varenicline and risk of psychiatric conditions, suicidal behaviour, criminal offending, and transport accidents and offences: population based cohort study. BMJ 2015;350:h2388.

[61] Kotz D, Viechtbauer W, Simpson C, van Schayck OCP, West R, Sheikh A. Cardiovascular and neuropsychiatric risks of varenicline: a retrospective cohort study. Lancet Respir Med 2015 Oct;3(10):761-8. doi: 10.1016/S2213-2600(15)00320-3.

Appendix 1. Lexicon of MedDRA Terminology

All adverse event data presented in this document were coded using the Medical Dictionary for Regulatory Activities (MedDRA). MedDRA is a highly standardized medical terminology dictionary developed by the International Conference on Harmonization to facilitate international sharing of information regarding medicinal products with regulatory authorities.[62]

MedDRA Coding Hierarchy

There are five levels to the MedDRA coding hierarchy, arranged from very specific to very general and they include: Lowest Level Terms (LLTs), Preferred Terms (PTs), High Level Terms (HLTs), High Level Group Terms (HLGTs), and System Organ Classes (SOCs).

LLTs are the most specific level and these terms parallel how information is communicated and reflect how an observation might be reported in practice.

PTs are each a distinct descriptor (single medical concept) for a symptom, sign, disease diagnosis, therapeutic indication, investigation, surgical or medical procedure, and medical social or family history characteristic.

HLTs are groupings of related PTs based upon anatomy, pathology, physiology, etiology or function.

HLGTs are groupings of HLTs related to each other by anatomy, pathology, physiology, etiology or function.

SOCs are groupings of HLGTs based on etiology, manifestation site or purpose.

As an example:

LLTs= Cotton wool in head, Feeling abnormal, Feeling bad, Feeling dazed, Feeling floating, Feeling lifeless, Feeling miserable, Feeling stoned, Feeling strange, Feeling weightless, Feels awful, Feels bad, Feels poorly, Felt like a zombie, Floating feeling, Foggy feeling in head, Funny episode, Fuzzy, Fuzzy head, Muzzy head, Neck strange feeling of, Soft feeling, Spaced out, Thick head, Unstable feeling, Weird feeling

PT=Feeling abnormal

HLT=Feelings and cessations NEC

HLGT=General systems and disorders NEC

SOC= General disorders and administration site conditions

[62] Medical Dictionary for Regulatory Activities, http://www.meddra.org/ [accessed 1 July 2016].

Appendix 2. Mechanism of Action and Biological Plausibility

Varenicline binds with high affinity and selectivity to α4β2 and α6β2-containing (α6β2*) nAChRs (inhibition constants [Ki]=0.1-0.4 nM), and acts as a partial agonist with 10%-45% agonist efficacy relative to acetylcholine. The α4β2 nAChR subtype has been shown to play a key role in mediating the addictive effects of nicotine, which also binds selectively with high affinity to this receptor subtype. Pharmacologically relevant concentrations of varenicline result in a functional interaction with human α4β2 nAChRs, causing extensive desensitization and low-level activation of α4β2 nAChRs.[63,64] This pharmacological profile of varenicline is comparable to that of nicotine at concentrations found in smokers, suggesting that, functionally, varenicline may substitute for nicotine during abstinence. Like nicotine, varenicline increases mesolimbic dopamine release but to a lesser extent, and reduces nicotine self-administration after oral dosing in rats. Varenicline therefore reduces craving induced by the absence of nicotine during a quit attempt, but without the abuse liability associated with a full agonist like nicotine. In addition, since varenicline has higher binding affinity than nicotine for α4β2 nAChRs, it can prevent inhaled nicotine from binding to the target receptor during a relapse, thereby reducing the subjective feelings of reward normally obtained from smoking.

Results of in vitro binding studies and in vivo nonclinical investigations on the effect of varenicline on neurotransmitter release and in CNS behavioral assays provide no pharmacological mechanism that can explain how varenicline use would trigger serious NPS adverse events. In addition, the nonclinical profile of varenicline is comparable to that of nicotine at concentrations in the range of human exposures during treatment with NRT, which is not associated with serious NPS adverse events. Data from nonclinical assays are summarized in the following sections.

Binding Affinities

Varenicline is highly selective for α4β2 and α6β2* neuronal nAChRs with substantially lower binding affinities for other nAChRs and demonstrates no pharmacologically relevant binding (at least 850-fold lower affinity) to other biological targets (ion channels, transmitter receptors, transporters and enzymes) that have been implicated in CNS disorders and thereby serious NPS adverse events. This includes dopaminergic, serotonergic, adrenergic, GABA-ergic and glutamatergic receptors and transporters, and neurokinin, opioid and cannabinoid receptors, and enzymes such as monoamine oxidase-A (MAO-A).[65]

Table 34. In Vitro Affinities and Inhibitory Potencies of Varenicline at Selected Human receptors, Ion Channels, Transporters and Enzymes

Nicotinic nAChR subtypes[a]		Transmitter receptors[b]	
α4β2	0.4	Dopaminergic	>1,000
α6β2* *(mouse)*	5.5	Alpha-Adrenergic	>10,000
α3β4	86	Beta-Adrenergic	>10,000
α7	125	Serotonergic	>1,000
α1β1γδ	8,200	Histaminergic	>1,000

Table 34. In Vitro Affinities and Inhibitory Potencies of Varenicline at Selected Human receptors, Ion Channels, Transporters and Enzymes

		GABA-ergic	>1,000
Ion Channels[b]		Glutamatergic	>1,000
Calcium	>1,000	Cannabinoid	>1,000
Sodium	>1,000	Opioid	>1,000
Potassium	>1,000	Neurokinin	>1,000
$GABA_{Cl}$	>1,000		
hERG [c]	>10,000	**Transmitter transporters**[b]	
Serotonin ($5HT_3$)	350	Dopamine	>1,000
		Norepinephrine	>1,000
Enzymes[b]		Serotonin	>1,000
MAO-A	>1,000	Gamma-aminobutyric	>1,000
Protein Kinase	>1,000	Choline	>1,000
Cytochrome	>1,000	Glutamate	>1,000

α6β2*=α6β2-containing.
[a] Binding affinities (K_i) in nM
[b] Inhibitory concentrations (IC_{50}) in nM (values >1,000 or >10,000 indicate no significant inhibition of radioligand binding at test concentrations of 1 or 10 μM)
[c] hERG = human ether-à-go-go related gene
Data from Rollema et al 2007[66], 2010[63], 2014[67]; Grady et al 2010[64], US FDA CDER 2006 (Chantix NDA)[68]

Effects on Neurotransmitter Release

Varenicline's effects on neurotransmitter release as measured by microdialysis in the brain from freely moving rats are consistent with its binding profile, in that changes in neurotransmitter release are mediated via nAChRs, not via blocking reuptake sites or enzymatic breakdown. It is thus unlikely that varenicline administration would result in NPS AEs due to excessive increases or depletions of key neurotransmitters. Low doses of varenicline (0.03-1 mg/kg) cause a modest increase in mesolimbic dopamine release in rat nucleus accumbens via its interaction with α4β2 and α6β2 containing nAChRs; this mechanism underlies its efficacy as a smoking cessation aid.[66] In addition, microdialysis studies in rat prefrontal cortex show that at pharmacologically relevant doses (≤1 mg/kg), varenicline does not significantly modulate the release of cortical neurotransmitters, such as dopamine, norepinephrine, serotonin and ACh. In general, the mesolimbic neurochemical effects of varenicline are smaller than induced by nicotine from smoking and more or less comparable to nicotine from NRT.[69] Because varenicline and nicotine do not inhibit transmitter reuptake sites, vesicular transporters or metabolic enzymes, neither drug will deplete transmitter stores (<10% of control) or cause large transmitter increases (>1,000% of control), which have been associated with the neurotoxic effects of, for example, reserpine and methamphetamine, respectively.

Animal Behavioral Tests

Nonclinical safety studies that were conducted during the development of varenicline, and described in the Chantix NDA[68], did not detect adverse behavioral effects or neurological signs at pharmacologically relevant exposures of varenicline. These studies included acute safety pharmacology studies in mice, repeat-dose toxicity studies in mice, rats, dogs and cynomolgus monkeys, and a pre- and postnatal development study in rats. In acute safety pharmacology and repeat-dose toxicity studies, the effects of a wide range of varenicline doses were investigated, including doses that resulted in several fold higher exposures than in patients receiving 1 mg BID varenicline, without causing neurological deficits.

Since market approval, varenicline has been investigated in a variety of animal behavioral tests that are routinely used as translational models for the major CNS behavioral domains: mood, sensory gating and cognitive processing. The primary objective of the majority of these studies was to explore possible therapeutic benefits of varenicline and other α4β2 nAChR ligands for additional potential CNS indications, such as depression, cognitive deficits, alcohol dependence, and pain. However, if varenicline were causally related to a risk of serious NPS adverse events, doses of varenicline that attain or exceed the range of human exposures in smoking cessation would be expected to impair the behavioral performance in one or more of these CNS animal models. A comprehensive review of literature data from a wide variety of behavioral tests (Table 35) does not reveal a biological response for varenicline that would indicate potential to cause serious NPS adverse clinical events. Moreover, a comparison between the responses of varenicline and nicotine in these models, at nicotine doses that correspond to exposures in patients using NRT, indicates varenicline's responses are very similar to that of nicotine used in NRT, which has no risk identified for NPS adverse events.[70,71]

Table 35. Summary of Animal Behavioral Tests With Data for Varenicline and Nicotine by Behavioral Domain

CNS Domain	Animal Test	References
Mood	Forced Swim	[72, 73, 74, 75, 76, 77, 78]
	Elevated Plus Maze	[73, 79, 80, 81, 82]
	Elevated Zero Maze	[77, 79]
	Neo-Hypophagia	[77, 83]
	Marble Burying	[77, 83, 84, 85, 86, 87, 88]
Sensory Gating	Acoustic Startle	[73, 89, 90, 69]
	Prepulse Inhibition	[73, 90, 69, 91]
	Auditory Gating	[69, 92, 93, 94, 95]
Cognition	Novel Object Recognition	[69, 96, 97, 98]
	Morris Water Maze	[99, 100]
	5-Choice Serial Reaction Time Task	[101, 102, 103]
	Contextual Fear Conditioning	[104, 105, 106, 107, 108, 109]
	Sustained Attention	[69, 110]
	Delayed Matching to Sample	[111, 112, 113, 114]
	Histamine Release	[69]
	Theta Oscillations	[69, 115, 116]

Finally, several human clinical laboratory studies have also measured the effects of varenicline in the behavioral domains that have been evaluated in animal behavioral tests. The results of these human translational studies indicate that varenicline has either no effect or slightly improves, but does not impair, measures of mood,[117, 118, 119] sensory gating,[120, 121] and attention, memory, or learning[122, 123, 124, 125, 119, 126] in patients or volunteers.

Nonclinical Conclusions

In vitro studies demonstrate that varenicline has high selectivity for α4β2 and α6β2* subtypes of nAChRs and does not bind to targets that have been implicated in CNS disorders, and thereby associated with serious NPS adverse events. The results of in vivo studies demonstrate that varenicline neither excessively increases nor depletes the levels of key neurotransmitters and does not impair behavior in several animal tests that assess CNS functioning and effects on mood, sensory gating and cognitive processing. The in vitro and in vivo data also indicate that varenicline's nonclinical profile is comparable to that of nicotine used in NRT. The combined results of nonclinical studies have not identified an underlying pharmacological mechanism to explain the serious NPS adverse events.

[63] Rollema H, Shrikhande A, Ward K et al. Preclinical properties of varenicline, cytisine and dianicline, α4β2 nAChR partial agonists for nicotine dependence, translate to clinical efficacy. An in vitro and in vivo study. Brit J of Pharmacol 2010;160:334-5. doi: 10.1111/j.1476-5381.2010.00682.x.

[64] Grady SR, Drenan RM, Scott R. Breining SR et al. Structural differences determine the relative selectivity of nicotinic compounds for native a4b2*-, a6b2*-, a3b4*- and a7-nicotine acetylcholine receptors. Neuropharmacology 2010;58:1054-66.

[65] Bowes J, Brown AJ, Hamon J, Jarolimek W, Sridhar A, Waldron G, Whitbread S. Reducing safety-related drug attrition: the use of in vitro pharmacological profiling. Nat Rev Drug Disc 2012;11:909-22.

[66] Rollema H, Chambers LK, Coe JW et al. Pharmacological profile of the alpha4beta2 nicotinic acetylcholine receptor partial agonist varenicline, an effective smoking cessation aid. Neuropharmacology 2007;52(3):985-94.

[67] Rollema H, Russ C, Lee TC, et al. Functional interactions of varenicline and nicotine with nAChR subtypes implicated in cardiovascular control. Nicotine Tob Res 2014; 16(6):733-42. doi: 10.1093/ntr/ntt208. Epub 2014 Jan 9.

[68] US FDA, CDER. Drug Approval Package, Chantix (Varenicline) Tablets, Pharmacology Review, 2006. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021928_s000_Chantix_PharmR.pdf (accessed June, 2016).

[69] Rollema H, Hajós M, Seymour PA et al. Preclinical pharmacology of the α4β2 nAChR partial agonist varenicline related to effects on reward, mood and cognition. Biochem Pharmacol 2009;78:813-824. doi: 10.1016/j.bcp.2009.05.033.

[70] Mills EJ, Wu P, Lockhart I et al. Adverse events associated with nicotine replacement therapy (NRT) for smoking cessation. A systematic review and meta-analysis of one hundred and twenty studies involving 177,390 individuals. Tob Induc Dis 2010; 8:8.

[71] Fucito LM, Bars MP, Forray A et al. Addressing the evidence for FDA nicotine replacement therapy label changes: a policy statement of the Association for the Treatment of Tobacco use and Dependence and the Society for Research on Nicotine and Tobacco. Nicotine Tob Res 2014; 16(7):909-14.

[72] Caldarone BJ, Wang D, Paterson NE et al. Dissociation between duration of action in the forced swim test in mice and nicotinic acetylcholine receptor occupancy with sazetidine, varenicline, and 5-I-A85380. Psychopharmacology 2011;217(2):199-210. doi: 10.1007/s00213-011-2271-y.

[73] Kucinski A, Wersinger A, Ewa K. Stachowiaka EK et al. The effects of varenicline on sensory gating and exploratory behavior with pretreatment with nicotinic or 5-HT3A receptor antagonists. Behav Pharmacol 2015; 26:217-26.

[74] Rollema H, Guanowsky V, Mineur YS et al. Varenicline has antidepressant- like activity in the forced swim test and augments sertraline's effect. Eur Pharmacol 2009;605(1-3):114-6. doi: 10.1016/j.ejphar.2009.01.002.

[75] Suemaru K, Yasuda K, Cui R. Antidepressant-like action of nicotine in forced swimming test and brain serotonin in mice. Physiol Behav 2006;88:545-9.

[76] Tizabi Y, Overstreet DH, Rezvani AH et al. Antidepressant effects of nicotine in an animal model of depression. Psychopharmacology 1999;142:193-9.

[77] Turner JR, Castellano LM, Blendy JA. Nicotinic partial agonists, varenicline and sazetidine-a, have differential effects on affective behavior. J Pharmacol Exp Ther 2010;334(2):665-72. doi: 10.1124/jpet.110.166280.

[78] Vázquez-Palacios G, Bonilla-Jaime H, Velázquez-Moctezuma J. Antidepressant-like effects of the acute and chronic administration of nicotine in the rat forced swimming test and its interaction with fluoxetine. Pharmacol Biochem Behav 2004;78:165-9.

[79] Braun AA, Skelton MR, Vorhees CV. Comparison of the elevated plus and elevated zero mazes in treated and untreated male Sprague-Dawley rats: Effects of anxiolytic and anxiogenic agents. Pharmacol Biochem Behav 2011;97(3):406-15.

[80] Kruk-Słomka M, Budzyńska B, Biała G. Involvement of cholinergic receptors in the different stages of memory measured in the modified elevated plus maze test in mice. Pharmacol Reports 2012;64:1066-80.

[81] McGranahan TM, Patzlaff NE, Grady SR et al. alpha4beta2 nicotinic acetylcholine receptors on dopaminergic neurons mediate nicotine reward and anxiety relief. J Neurosci 2011;31:10891-902.

[82] Varani AP, Moutinho LM, Bettler B, Balerio GN. Acute behavioural responses to nicotine and nicotine withdrawal syndrome are modified in GABA(B1) knockout mice. Neuropharmacology 2012; 63:863-72.

[83] Turner JR, Wilkinson DS, Poole RLF et al. Divergent functional effects of sazetidine-A and varenicline during nicotine wWithdrawal. Neuropsychopharmacol 2013;38:2035-47.

[84] Anderson SM, Brunzell DH. Low dose nicotine and antagonism of b2 subunit containing nicotinic acetylcholine receptors have similar effects on affective behavior in mice. PLoS ONE 2012;7(11): e48665.

[85] Egashira N, Abe M, Shirakawa A et al. Effects of mood stabilizers on marble-burying behavior in mice: involvement of GABAergic system. Psychopharmacol 2013;226(2):295-305.

[86] Kim J-W, Seung H, Kwon KJ et al. Subchronic treatment of donepezil rescues impaired social, hyperactive, and stereotypic behavior in valproic acid-induced animal model of autism. PLos One 2014;9(8): e104927.

[87] Moy SS, Nonneman RJ, Shafer GO. Disruption of social approach by MK-801, amphetamine, and fluoxetine in adolescent C57BL/6J mice. Neurotoxicol Teratol 2013;36:36-46.

[88] Turner JR, Castellano LM, Blendy JA. Parallel anxiolytic-like effects and upregulation of neuronal nicotinic acetylcholine receptors following chronic nicotine and varenicline. Nic Tob Res 2011;13(1):41-46. doi: 10.1093/ntr/ntq206.

[89] Decker MW, Bannon AW, Curzon P, Gunther KL et al. ABT-089 [2-methyl-3-(2-(S)-pyrrolidinylmethoxy)pyridine dihydrochloride]: II. A novel cholinergic channel modulator with effects on cognitive performance in rats and monkeys. J Pharmacol Exp Ther 1997;283(1):247-58.

[90] Goktalay T, Buyukuysal S, Uslu G et al. Varenicline disrupts prepulse inhibition only in high-inhibitory rats. Prog Neuropsychopharmacol Biol Psychiatry 2014;53:54-60. doi: 10.1016/j.pnpbp.2014.03.001. Epub 2014 Mar 13.

[91] Andreasen JT, Andersen KK, Nielsen EØ, Mathiasen L, Mirza NR. Nicotine and clozapine selectively reverse a PCP-induced deficit of PPI in BALB/cByJ but not NMRI mice: comparison with risperidone. Behav Brain Res 2006;167(1):118-27.

[92] Radek RJ, Miner HM, Bratcher NA et al. α4β2 Nicotinic receptor stimulation contributes to the effects of nicotine in the DBA/2 mouse model of sensory gating. Psychopharmacology 2006;187:47–55.

[93] Rudnick ND, Strasser AA, Phillips JM et al. Mouse model predicts effects of smoking and varenicline on event-related potentials in humans. Nicotine Tob Res 2010;12(6):589-97. doi: 10.1093/ntr/ntq049.

[94] Stevens KE, Wear KD. Normalizing effects of nicotine and a novel nicotinic agonist on hippocampal auditory gating in two animal models. Pharmacol Biochem Behav 1997;57(4): 869–74.

[95] Wildeboer-Andrud KM, Stevens KE. The smoking cessation drug varenicline improves deficient P20-N40 inhibition in DBA/2 mice. Pharmacol Biochem Behav 2011;100(1):17-24. doi: 10.1016/j.pbb.2011.07.001.

[96] Kruk-Słomka M, Michalak A, Budzyñska B et al. A comparison of mecamylamine and bupropion effects on memory-related responses induced by nicotine and scopolamine in the novel object recognition test in mice. Pharmacol Reports 2014;66: 638–46.

[97] Puma C, Deschaux O, Molimard R et al. Nicotine improves memory in an object recognition task in rats. Eur Neuropsychopharmacol 1999:9:323-27.

[98] Tian S, Pan S, You Y. Nicotine enhances the reconsolidation of novel object recognition memory in rats. Pharmacol Biochem Behav 2015;129:14-18.

[99] King J, Huang W, Wei Chen W et al. A comparison of brain and behavioral effects of varenicline and nicotine in rats. Behav Brain Res 2011;223(1):42-7. doi: 10.1016/j.bbr.2011.04.012.

[100] Socci DJ, Sanberg PR, Arendash GW. Nicotine enhances Morris Water Maze performance of young and aged rats. Neurobiol Aging 1995;16(5):857-60.

[101] Baarendse PJJ, Vanderschuren LJMJ. Dissociable effects of monoamine reuptake inhibitors on distinct forms of impulsive behavior in rats. Psychopharmacol 2012;219:313-26.

[102] Van Gaalen MM, Brueggeman RJ, Bronius PF et al. Behavioral disinhibition requires dopamine receptor activation. Psychopharmacology (Berl). 2006;187(1):73-85.

[103] Wouda JA, Riga D, De Vries W et al. Varenicline attenuates cue-induced relapse to alcohol, but not nicotine seeking, while reducing inhibitory response control. Psychopharmacology (Berl) 2011;216(2):267-77. doi: 10.1007/s00213-011-2213-8.

[104] Gould TJ, Higgins JS (2003) Nicotine enhances contextual fear conditioning in C57BL/6J mice at 1 and 7 days post-training. Neurobiol Learn Mem 80:147-57.

[105] Gould TJ, Lommock JA. Nicotine enhances contextual fear conditioning and ameliorates ethanol- induced deficits in contextual fear conditioning. Behav Neurosci 2003;117(6):1276-82.

[106] Gould TJ, Wehner JM. Nicotine enhancement of contextual fear conditioning. Behav Brain Res 1999;102: 31–9.

[107] Gulick D, Gould TJ. Varenicline ameliorates ethanol-induced deficits in learning in C57BL/6 mice. Neurobiol Learn Mem 2008;90(1):230-6.

[108] Raybuck JD, Portugal GS, Lerman C et al. Varenicline ameliorates nicotine withdrawal-induced learning deficits in C57BL/6 mice. Behav Neurosci 2008;122(5):1166-71. doi: 10.1037/a0012601.

[109] Wehner JM, Keller JJ, Keller AB, et al. Role of neuronal nicotinic receptors in the effects of nicotine and ethanol on contextual fear conditioning. Neurosci 2004;129:11-24.

[110] Howe WM, Ji J, Vinay Parikh V et al. Enhancement of attentional performance by selective stimulation of a4b2* nAChRs: underlying cholinergic mechanisms. Neuropsychopharmacol 2010;35:1391-401

[111] Buccafusco JJ, Jackson WJ. Beneficial effects of nicotine administered prior to a delayed matching-to-sample task in young and aged monkeys. Neurobiol Aging 1991;12:233-8.

[112] Katner SN, Davis SA, Kirsten AJ, Taffe MA. Effects of nicotine and mecamylamine on cognition in rhesus monkeys. Psychopharmacology 2014;175:225-40.

[113] Terry AV, Buccafusco JJ, Jackson WJ. Scopolamine reversal of nicotine enhanced delayed matching-to-sample performance in monkeys. Pharmacol Biochem Behav 1993;45:925-9.

[114] Terry AV, Plagenhoef M, Callahan PM. Effects of the nicotinic agonist varenicline on the performance of tasks of cognition in aged and middle-aged rhesus and pigtail monkeys. Psychopharmacol 2016;233(5):761-71. DOI 10.1007/s00213-015-4154-0.

[115] Hoffmann WE, Scott L, Harvey BD et al. Varenicline improves auditory gating and augments hippocampal theta oscillation in rats. 2008; Poster 436.4/I10 2008 SfN Mtg Planner, Washington DC.

[116] Lu CB, Li CZ, Li DL, Henderson Z. Nicotine induction of theta frequency oscillations in rodent medial septal diagonal band in vitro. Acta Pharmacol Sinica 2013:34:819-29.

[117] Patterson F, Jepson C, Strasser AA et al. Varenicline improves mood and cognition during smoking abstinence. Biol Psychiatry. 2009; 65(2):144–9.

[118] McKee 2012 McKee SA, Weinberger AH, Shi J et al. Developing and validating a human laboratory model to screen medications for smoking cessation. Nicotine Tob Res 2012;14(11):1362–71.

[119] Mocking RJT, Pflanz CP, Pringle AP et al. Effects of short-term varenicline administration on emotional and cognitive processing in healthy, non-smoking adults: a randomized, double-blind, study. Neuropsychopharmacology 2013;38:476–84.

[120] Rudnick et al 2010 Rudnick ND, Strasser AA, Phillips JM et al. Mouse model predicts effects of smoking and varenicline on event-related potentials in humans. Nic Tob Res 2010;12(6):589-97. doi: 10.1093/ntr/ntq049.15

[121] Hong L, Thaker GK, McMahon et al. Effects of moderate-dose treatment with varenicline on neurobiological and cognitive biomarkers in smokers and nonsmokers with schizophrenia or schizoaffective disorder. Arch of Gen Psychiatry 2011;68(12):1195-206. doi: 10.1001/archgenpsychiatry.2011.83. Epub 2011 Aug 1.

[122] Smith RC, Lindenmayer J-P, Davis JM et al. Cognitive and antismoking effects of varenicline in patients with schizophrenia or schizoaffective disorder. Schizophrenia Res 2009;110(1):149-55.

[123] Loughead J, Ray R, Wileyto EP et al. Effects of the alpha4beta2 partial agonist varenicline on brain activity and working memory in abstinent smokers. Biol Psychiatry 2010;67(8):715-21. doi: 10.1016/j.biopsych.2010.01.016. Epub 2010 Mar 6.

[124] Ashare RL, McKee SA. Effects of varenicline and bupropion on cognitive processes among nicotine-deprived smokers. Exp Clin Psychopharmacol 2012;20(1):63–70. doi:10.1037/a0025594.

[125] Ashare RL, Falcone M, Lerman C. Cognitive function during nicotine withdrawal: Implications for nicotine dependence treatment. Neuropharmacology 2013;76: 581-91.

[126] Mocking RJT, Wever SA, Pflanz CP et al. Effects of short-term varenicline administration on cortisol in healthy, non-smoking adults: a randomized, double-blind, study. Psychopharmacology 2014;231:143–8.

Appendix 3. Literature Review of Non-Pfizer Randomized, Controlled Clinical Trials Reporting on NPS Events

2014 Literature Review of Non-Pfizer Randomized, Controlled Clinical Trials Reporting on NPS Events

A literature search to identify double–blind, randomized, controlled trials or meta-analyses of randomized, controlled trials that reported NPS safety results for varenicline vs placebo or another comparator was conducted. The following databases were searched (using a cut-off date of 25 February 2014) for varenicline and various NPS keywords and mental disorders subject headings: Ovid Medline, Embase, Embase Daily Alerts and Derwent Drug File. The search terms were based on NPS terms that are included in the US CHANTIX label and included: psychiatric, neuropsychiatric, mental disorders, suicide, suicidal ideation, suicidal behavior, suicide attempt, self harm, depression, depressive disorder, depressed mood, mood disorder, schizophrenia, hallucination, delusion, psychosis, paranoia, mania, bipolar disorder, anxiety, panic, agitation, aggression, hostility, abnormal behavior, abnormal thinking, and personality disorder. Preclinical publications, conference literature, and other publication types such as notes, comments, editorials and non-English language publications were excluded during the search process. Studies in non-smokers, populations using varenicline for indications other than smoking cessation, studies in which all patients received varenicline, studies of less than 20 patients treated with varenicline and publications not reporting original data or new analysis (such as review articles) were excluded during the review of the search results.

The review of the literature identified 10 relevant publications matching the search objective. Of these 10 publications, 4 publications included results from 3 meta-analyses (2 publications reported on the same Cochrane meta-analysis) and 6 were clinical trials. Only NPS results were summarized below for these 9 publications.

The 3 meta-analyses (Cahill, Gibbons, Huang), found no evidence of increased NPS risk with varenicline when compared with placebo.

The first meta-analysis (Cahill[127,128]) was based on 14 varenicline double-blind, randomized, controlled trials (of which 13 were Pfizer sponsored) and included 3,984 varenicline and 2,349 placebo patients. The subgroup analysis of NPS SAEs yielded an RR of 0.53 (95% CI: 0.17 – 1.67) for varenicline vs placebo.

The second meta-analysis (Gibbons et al[129]) studied the NPS safety of varenicline using person level AE data from 17 randomized placebo-controlled trials (4,823 varenicline and 3204 placebo patients) of varenicline conducted by Pfizer. The results revealed the overall effect of varenicline on suicidal thoughts and behavior (odds ratio (OR): 0.57; 95% CI: 0.23-1.38), depression (OR: 1.01, 95% CI: 0.68-1.52), and aggression/agitation (OR=1.27, 95% CI: 0.85–1.92) was not significant. Psychiatric illness did not moderate the effect of varenicline for any of these symptoms. Having a current or past psychiatric illness increased the risk of NPS events equally in varenicline treated and placebo patients.

The third meta-analysis (Huang et al[130]) included 10 randomized controlled varenicline trials (6,375 smokers), all conducted by Pfizer. The analysis found there was not sufficient evidence that varenicline was associated with an increased risk of psychiatric AEs compared with placebo (RR: 1.45, 95% CI: 0.90-2.32).

Of the 6 clinical trial publications, 2 publications involved patients with psychiatric co-morbidities. The first study (Evins et al[131]) was a randomized, double-blind, placebo-controlled, relapse–prevention trial in smokers with schizophrenia or bipolar disorder. In the open-label phase, 203 smokers received 12 weeks varenicline. At Week 12, 87/203 (43%) subjects had 2 weeks or more of continuous abstinence and were randomized to varenicline or placebo from Weeks 12-52. The study utilized psychiatric scales, including the Brief Psychiatric Rating Scale (BPRS) and Calgary Depression Scale for Schizophrenia and found there was no effect of treatment assignment on severity of psychiatric symptoms. Although the study was not powered to detect changes in psychiatric symptoms, the authors stated "…we detected no signal for varenicline to be associated with new or worsening neuropsychiatric symptoms". The second study (Hong et al[132]) was a double-blind, randomized, placebo-controlled trial of smokers and non-smokers with schizophrenia or schizoaffective disorders that evaluated the effects of varenicline on neurobiological and cognitive biomarkers. The study included a total of 69 smokers and non-smokers and utilized several psychiatric scales. With regards to the BPRS total, there were no significant treatment or interaction effects with a trend towards reduced psychiatric symptoms for varenicline vs placebo ($F_{1,54.2} = 3.32$, $p=0.07$). The BPRS psychosis subscale showed a trend towards reduced psychosis in the varenicline group compared to the placebo group ($F_{1,58} = 3.89$, $p=0.053$). There were no differences in treatment effects in smokers vs non-smokers (all $p \geq 0.30$). There were no significant effects of treatment on negative symptoms assessed using the Schedule for Assessment of Negative Symptoms, or on depression, which was assessed using the HAM-D. Assessments of depression, anxiety and suicidality were further probed via Item 3 of HAM-D (suicidality), Item 13 of the BPRS (depression) and the BPRS anxiety rating; all of which showed no treatment effect. Hence, there was no evidence that treatment with slowly titrated varenicline at 1 mg/day increased any of these measures.

In the remaining 4 clinical study publications, 2 (McClure, Steinberg) involved comparisons of varenicline to placebo and 2 (Stein, Cincirpini) involved an active comparator as well. These studies ranged in size from 47 to 315 subjects. Of these 4 studies, Cinciripini et al[133] used several psychiatric scales including the Positive and Negative Affect Schedule, Wisconsin Smoking Withdrawal Scale, and the Center for Epidemiological Studies Depression Scale. The study specifically examined the effect of varenicline vs bupropion SR on smoking cessation and emotional functioning. The study found that varenicline use was associated with a generalized suppression of depression when compared with the other treatments, while both bupropion and varenicline improved concentration and decreased negative affect and sadness when compared with placebo, while having little effects on anxiety and anger. In addition, no significant differences were noted for any of the psychiatric or neurological AEs between treatment arms. The second study (Stein[134]) compared varenicline, NRT and placebo for smoking cessation in methadone maintained smokers and reported that smokers on varenicline tended to be less likely to report anger, irritability, frustration or anxiety related events during the initial month of treatment. Two participants in the varenicline arm stopped study medication due to neurobehavioral adverse

effects. The third study (Steinberg[135]), which compared varenicline vs placebo in hospitalized smokers, reported at a 4-week outpatient follow-up visit of a decrease in MNWS of 1.45 points in the varenicline group compared with a 0.11 increase in the placebo group, this difference was not statistically significant. Depression was reported in 5 patients in both groups, which was not a statistically significant difference. The fourth study (McClure[136]) compared the relapse prevention effects of varenicline vs placebo following a programmed lapse, which occurred on the second day of the quit attempt. This study reported that subjective assessments measured on withdrawal (MNWS) and mood (PANSS) were not sensitive to medication effects but showed an effect of time, with ratings decreasing over time in both groups.

The review of the literature identified 3 meta-analyses and 6 double-blind, randomized, controlled trials that reported on NPS safety for varenicline when used in smokers. None of these publications reported evidence of an increased NPS risk with varenicline.

Meta-Analyses and Other Pooled/Combined Analyses of Randomized Controlled Trials

Summarized below are the 6 meta-analyses and other pooled/combined analyses of randomized controlled trials identified in the updated literature search.

The **Thomas et al**[137] analysis included 39 RCTs involving 5817 varenicline and 4944 placebo treated subjects. The analysis found 2 varenicline subjects died by suicide and 4 attempted suicide (2 in the varenicline arm and 2 in the placebo arm). Thirty one trials reported suicide and suicide attempt and the Peto OR for varenicline vs. placebo was 1.67 (95% confidence interval (CI) 0.33 to 8.57; P=0.54, I^2=10.3%) and the risk difference (RD) was 0.0003 (−0.002 to 0.003; P=0.81, I^2=0.0%). Twenty trials reported suicidal ideation and the Peto OR was 0.58 (0.28 to 1.20; P=0.14, I^2=0.0%) and the RD was −0.003 (−0.009 to 0.002; P=0.24, I^2=0.0%). Thirty one trials reported on depression and the Peto OR was 0.96 (0.75 to 1.22; P=0.74, I^2=0.0%) and RD was −0.001 (−0.01 to 0.01; P=0.74, I^2=0.0%). Death was reported in 36 trials (varenicline: 13/5760, placebo: 11/4887). The Peto OR for death was 1.05 (0.47 to 2.38; P=0.9, I^2=38.7%), and there was no evidence of an increased risk of death in the varenicline group compared with the placebo group (RD 0.0001, −0.003 to 0.003; P=0.94, I^2=0.0%). There was no evidence of an increased risk of irritability, aggression, or somnolence as the CI included the null value of 1. Varenicline was associated with some evidence of a reduced risk of anxiety (0.75, 0.61 to 0.93; P=0.008, I^2=5.7%). The authors concluded "this meta-analysis found no evidence of an increased risk of suicide or attempted suicide, suicidal ideation, depression or death with varenicline.

The **Foulds et al**[138] analysis examined weekly individual Minnesota Nicotine Withdrawal ScaleScale (MNWS) symptom ratings from 8 double-blind, RCT (all Pfizer sponsored) which included 2403 varenicline and 1434 placebo treated subjects. The analysis showed that the ratings for the NPS symptoms of depressed mood, irritability, frustration or anger, anxiety, restlessness, and difficulty concentrating peaked during the first or second week after the target quit date (TQD), before gradually returning to baseline levels at Week 5 or 6 for placebo-treated participants, and earlier for varenicline. For all these items, scores were significantly lower ($p < .01$) for varenicline than placebo at each of Weeks 1–6 and Week 11 after the TQD. Marked increases in symptom severity ratings for the 5 NPS symptoms

(depressed mood, irritability, anxiety, difficulty concentrating, and restlessness) were less frequent on varenicline than on placebo. The authors concluded "that use of varenicline while trying to quit smoking reduces and does not increase NPS symptoms such as depressed mood and irritability measured on the MNWS in smokers without current psychiatric disorders."

The **Avery et al**[139] analysis examined depressive symptoms from 2 smoking cessation studies, one conducted in 152 postmenopausal women who received placebo (n=95) or nicotine patch (n=57), and the other in 78 women who received varenicline. The study found that subjects taking varenicline reported lower scores on the Center for Epidemiologic Study Depression Scale (CESD) over all time periods compared to nicotine or placebo ($p<.010$). These differences between varenicline and the other treatments remained when controlling for lifetime history of major depressive disorder (MDD) indicating this was an independent effect. The authors concluded "varenicline does not increase depressive symptoms during smoking cessation in postmenopausal women without current MDD. Subjects with a lifetime history of MDD are susceptible to developing depressive symptoms during smoking cessation, regardless of pharmacologic aid."

The **Kishi et al**[140] analysis included 7 double-blind, RCTs (total n=439) on the effects of varenicline adjuvant therapy in subjects with schizophrenia (1 RCT was a Pfizer sponsored study and 1 RCT also included subjects with bipolar disorder). The NPS outcome for this analysis were symptoms of psychopathology (total, positive, negative, and depressive symptoms) which comprised of results from the Brief Psychiatric Rating Scale (BPRS), Positive and Negative Syndrome Scale (PANSS), Hamilton Rating Scale for Depression (HAM-D) , Calgary Depression Rating Scale and Beck Depression Inventory. The analysis found that varenicline adjuvant therapy failed to show superiority over placebo for any symptoms: overall, positive, negative or depressive. No significant differences between varenicline and placebo were detected for suicidal ideation and depression. The authors concluded that due to the "limited sample sizes of the available studies, future studies are needed with much larger sample sizes to ensure that these findings are generalizable".

The **Wu et al**[141] analysis included 8 RCTs of 398 participants with severe mental illness evaluating varenicline with placebo. The NPS analysis showed that there was no significant difference seen between varenicline (n=158) vs placebo (n=114) in terms of suicidal ideation, depressed mood, anxiety, and mood swings. The authors concluded that "there appears to be no clear evidence that varenicline was associated with an increased risk of neuropsychiatric or other adverse events compared with placebo".

The latest Cochrane analysis (**Cahill**[142]) on nicotine receptor partial agonists for smoking cessation, was based on 39 varenicline RCTs with 25,290 subjects, of whom 11,801 used varenicline, 7109 placebo, 3445 NRT, and 2935 used bupropion with minimum 6 months follow-up. A number of different analyses sing various studies were conducted by Cochrane. One meta-analysis of studies which included EAGLES evaluating specific NPS AEs demonstrated a RR for depression of 0.94 (95% CI 0.77 to 1.14; 36 studies, 16,189 subjects, I^2=0%), with non-significantly lower rates in the varenicline groups. The RR for suicidal ideation was 0.68 (95% CI 0.43 to 1.07; 24 studies; 11,193 subjects, I^2=0%), with border-line non-significantly lower rates in the varenicline groups. Another meta-analysis evaluating

NPS SAEs (in 23 studies not including EAGLES) demonstrated a RR of 0.82 (95% CI 0.57 to 1.19). The authors conclude that "early reports of possible links to suicidal ideation and behavior have not been confirmed by current research".

Randomized Controlled Trials

Summarized below are the 7 randomized controlled trials identified in the updated literature search.

The following 3 of the 7 publications did not recruit subjects with a specific psychiatric disorder.

The **Nahvi et al**[143] study was a 24-week, double-blinded, placebo-controlled trial in which 112 smokers enrolled in methadone maintenance treatment program were randomized to varenicline (n=57) or placebo (n=55) for 12 weeks of treatment. NPS safety results found incident major depressive (2 varenicline and 1 placebo subjects) or manic episodes (no subjects) or psychotic disorders (1 varenicline and 3 placebo subjects) were infrequent, and did not differ between treatment arms [OR = 1.00, 95% CI = 0.4, 2.3]. During the intervention period, a small number of subjects reported non-specific wishes to be dead, only 1 in each treatment arm had thoughts of killing themselves and none had suicidal ideation with plan or intent. There was no difference in odds of suicidal ideation between treatment arms (OR = 0.88, 95%CI = 0.2, 3.9). The authors did not observe an association between varenicline and adverse psychiatric effects.

The **Eisenberg et al**[144] study was a multi-center, double-blind, randomized, placebo-controlled trial in 302 hospitalized smokers with an acute coronary syndrome (ACS) evaluating varenicline (n=151) compared with placebo (n=151) for 12 weeks on smoking abstinence. Patients with a history of NPS disorders were excluded. The study was not powered to examine safety endpoints, but was designed to describe the occurrence of SAEs in this population during treatment and follow-up. There were no cases of suicidal ideation in the study. A single NPS event involving hospitalization for depression occurred in a patient 25 days after taking one dose of varenicline. Similar numbers of patients in each treatment arm discontinued study treatment within 30 days because of AEs.

The **Lerman et al**[145] study was a nicotine metabolite ratio (NMR) stratified placebo-controlled randomized trial where 1246 smokers were randomly assigned by baseline NMR status to 11 weeks of placebo (placebo pill and patch) , nicotine patch (active patch, placebo pill) or varenicline (active pill, placebo patch). An NMR-by-treatment interaction showed that slow (*vs* normal) metabolizers reported greater overall side-effect severity with varenicline versus placebo (β=1.06, 95% CI: - 2.08 to –0.03; p=0.044). This reflected greater summary side-effects reported on varenicline (*vs* placebo) for slow metabolizers (β=0.61, 95% CI –0.10 to 1.32; p=0.09), but not for normal metabolizers (β=–0.44, 95% CI –1.19 to 0.30; p=0.24). Descriptive analysis showed that, in slow metabolizers, varenicline led to significant increases in abnormal dreams ($\chi 2$=13.0, p=0.005); in normal metabolizers, varenicline led to decreases in irritability ($\chi 2$=15.4, p=0.001), anxiety ($\chi 2$=11.2, p=0.01), and attentional disturbance ($\chi 2$=11.3, p=0.01). There were no NMR-by-treatment interactions for

withdrawal symptoms (p>0.10). The authors concluded that treating normal metabolizers with varenicline and slow metabolizers with nicotine patch could minimize side effects.

The remaining 4 publications recruited subjects with a specific psychiatric co-morbidity.

The **Chengappa et al**[146] study was a double-blind, placebo controlled trial conducted in smokers with DSM-IV bipolar disorder in which 31 subjects were randomized to varenicline and 29 were to placebo. At each visit, mood, anxiety symptoms, and illness severity were evaluated using the Montgomery-Asberg Depression Rating Scale (MADRS), Young Mania Rating Scale (YMRS), Hamilton Anxiety Rating Scale (HARS), and Clinical Global Impressions Scale (CGI) for which results as a group reflected a bipolar patient group that was euthymic at study entry and remained stable throughout the study regardless of treatment assignment. Suicidal thinking and behavior was also evaluated at each visit using the Columbia Suicide Severity Rating Scale (C-SSRS) and identified 8 instances of suicidal ideation in the varenicline group (vs 5 in the placebo group, a non-significant difference) which all occurred in patients that had a lifetime history of suicidal ideation. Depressed mood trended higher in varenicline (n=8) vs placebo (n=2); Fisher exact test, P= 0.08. Authors concluded that "vigilance for NPS adverse events is prudent when initiating varenicline for SC in this patient population."

The **Shim et al**[147] study was a randomized, double blind, placebo-controlled 8 week trial that examined the varenicline effect on cognitive impairments in 60 smokers and 60 non-smokers with schizophrenia. The study utilized several scales for which results showed no significant main effects of treatment or time by treatment arm interactions in the PANSS and SANS or CGI severity. Two patients each in varenicline and placebo groups showed aggravated psychotic symptoms and were withdrawn from the study. No subject in either group had increases in depressive symptoms measured by HAM-D.

The **Tulloch et al**[148] study was an open-label study evaluating smoking abstinence in 737 subjects with and without a psychiatric history. The study compared standard nicotine patch (for 10 weeks; n=245) with extended use of combination nicotine replacement therapy (patch plus gum or inhaler up to 22 weeks; n=245) and varenicline (up to 24 weeks; n=247). 59% of subjects had a lifetime psychiatric diagnosis. The NPS findings showed no significant differences in NPS AEs (such as anxiety, concentration and suicidal ideation) among treatment arms or between the psychiatric and non-psychiatric cohort. No difference in serious AEs or treatment discontinuations was observed between the groups. This study, while open-label, has been included in this literature review for completeness due to its similar study objectives to EAGLES.

The **Smith et al**[149] study was an 8-week, double-blind, randomized trial evaluating varenicline 2 mg/day (n=42) to placebo (n=45) in patients with DSM-IV diagnosis of schizophrenia or schizoaffective disorder. Varenicline subjects did not show any worsening of psychopathology scores, including positive symptoms and depression as determined by PANSS, SANS, and Calgary scales. No increase was found in any component of psychiatric symptoms with varenicline. No subject reported a clear increase of suicidal ideation and no suicides or new emergency acute depressive episodes occurred.

[127] Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database of Systematic Reviews 2013, Issue 5. Art. No.: CD009329. doi: 10.1002/14651858.CD009329.pub2

[128] Cahill K, Stevens S, Lancaster T. Pharmacological treatments for smoking cessation. JAMA 2014;311(2):193-4. Doi: 10.1001/jama.2013.283787

[129] Gibbons RD, Mann JJ. Varenicline, smoking cessation, and neuropsychiatric adverse events. Am J Psychiatry. 2013;170(12):1460-7. doi: 10.1176/appi.ajp.2013.12121599

[130] Huang Y, Li W, Jiang Y, et al. Long-term efficacy and safety of varenicline for smoking cessation: A systematic review and meta-analysis of randomized controlled trials. J Public Health (Germany) 2012; 20(4): 355-65.

[131] Evins AE, Cather C, Pratt SA, et al. Maintenance treatment with varenicline for smoking cessation in patients with schizophrenia and bipolar disorder: a randomized clinical trial. JAMA. 2014;311(2):145-54. doi: 10.1001/jama.2013.285113

[132] Hong LE, Thaker GK, McMahon RP, et al. Effects of moderate-dose treatment with varenicline on neurobiological and cognitive biomarkers in smokers and nonsmokers with schizophrenia or schizoaffective disorder. Arch Gen Psychiatry. 2011;68(12):1195-206.

[133] Cinciripini PM, Robinson JD, Karam-Hage M, et al. Effects of varenicline and bupropion sustained-release use plus intensive smoking cessation counseling on prolonged abstinence from smoking and on depression, negative affect, and other symptoms of nicotine withdrawal. JAMA Psychiatry 2013;27:1-12. doi:10.1001/jamapsychiatry.2013.678

[134] Stein MD, Caviness CM, Kurth ME, et al. Varenicline for smoking cessation among methadone-maintained smokers: A randomized clinical trial. Drug Alcohol Depend. 2013;133(2):486-93. doi: 10.1016/j.drugalcdep.2013.07.005

[135] Steinberg MB, Randall J, Greenhaus S, et al. Tobacco dependence treatment for hospitalized smokers: a randomized, controlled, pilot trial using varenicline. Addict Behav 2011;36(12):1127-32.

[136] McClure EA, Vandrey RG, Johnson MW, Stitzer ML. Effects of varenicline on abstinence and smoking reward following a programmed lapse. Nicotine Tob Res. 2013; 15(1):139-48. doi: 10.1093/ntr/nts101

[137] Thomas KH, Martin RM, Knipe DW et al. Risk of neuropsychiatric adverse events associated with varenicline: systematic review and meta-analysis. BMJ 2015;350:h1109 doi10.1136/bmj.h1109.

138 Foulds J, Russ C, Yu CR, et al. Effect of Varenicline on Individual Nicotine Withdrawal Symptoms: A Combined Analysis of Eight Randomized, Placebo-Controlled Trials. Nicotine Tob Res. 2013 Nov;15(11):1849-57. doi: 10.1093/ntr/ntt066

139 Avery N, Kenny AM, Kleppinger A, Brindisi J, Litt MD, Oncken CA. Effects of varenicline, nicotine or placebo on depressive symptoms in postmenopausal smokers. Am J Addict. 2014 Sep-Oct;23(5):459-65. doi: 10.1111/j.1521-0391.2014.12130.x.

140 Kishi T, Iwata N. Varenicline for Smoking Cessation in People with Schizophenia: Systematic Review and Meta-Analysis. Eur Arch Psychiatry Clin Neurosci 2016; 265:259-68.

141 Wu Q, Gilbody S, Peckham E, et al. Varenicline for smoking cessation and reduction in people with severe mental illnesses: systematic review and meta-analysis. Addiction 2016 ;Apr 4.

142 Cahill K, Lindson-Hawley N, Thomas KH, et al. Nicotine receptor partial agonists for smoking cessation. Cochrane Database of Systematic Reviews. 2016 May 9;(5):CD006103.

143 Nahvi S, Ning Y, Segal KS, et al. Varenicline efficacy and safety among methadone maintained smokers: A randomized placebo-controlled trial. Addiction. 2014 Sep;109(9):1554-63. doi: 10.1111/add.12631.

144 Eisenberg MJ, Windle SB, Roy N et al. Varenicline for smoking cessation in hospitalized patients with acute coronary syndrome. Circulation. 2016 Jan 05;133(1):21-30.

145 Lerman C, Schnoll RA, Hawk LW, et al. . Use of the nicotine metabolite ratio as a genetically informed biomarker of response to nicotine patch or varenicline for smoking cessation: a randomised, double-blind placebo-controlled trial. Lancet Respir Med. 2015 Jan 11. doi: 10.1016/S2213-2600(14)70294-2

146 Chengappa KNR, Perkins KA, Brar JS, et al. Varenicline for Smoking Cessation in Bipolar Disorder: A Randomized, Double-Blind, Placebo-Controlled Study. J Clin Psychiatry. 2014;75(7):765-72. doi: 10.4088/JCP.13m08756

147 Shim JC, Jung DU, Jung SS, Seo YS, Cho DM, Lee JH, Lee SW, Kong BG, Kang JW, Oh MK, Kim SD, McMahon RP, Kelly DL. Adjunctive varenicline treatment with antipsychotic medications for cognitive impairments in people with schizophrenia: a randomized double-blind placebo-controlled trial. Neuropsychopharmacology. 2012 Feb;37(3):660-8.

148 Tulloch HE, Pipe AL, Els C, et al. Flexible, dual-form nicotine replacement therapy or varenicline in comparison with nicotine patch for smoking cessation: a randomized controlled trial. BMC Med. 2016 Jun 7;14(1):80. doi: 10.1186/s12916-016-0626-2.

[149] Smith RC, Amiaz R, Si T-M, et al. Varenicline effects on smoking, cognition, and psychiatric symptoms in schizophrenia: A double-blind randomized trial. PLoS ONE. 2016 Jan 05;11 (1):e0143490.

Appendix 4. Observational Studies

Summary of Observational Studies Included in the Current CHANTIX Label

The Chantix USPI currently contains information from 4 observational cohort studies of selected serious NPS AEs, which are summarized in Table 36 below.

Table 36. Summary of Four Population-Based Observational Cohort Studies

Lead Author	Source Population	Study Period	Comparator	Primary Endpoint
Thomas	UK general practice	01Sep06 to 31Oct11	NRT	Fatal or non-fatal self-harm Pharmacologic treatment for depression
Pasternak	Population of Denmark	01Jan07 to 31Dec10	Bupropion	ED visit or inpatient admission for a psychiatric diagnosis within 30 days of treatment initiation
Meyer	US Military Health System	01Aug06 to 31Aug07	NRT	Primary inpatient discharge diagnosis for an NPS condition within 30 days of treatment initiation
Department of Veterans Affairs	US Veterans Health Administration	01May06 to 30Sep07	NRT	Primary inpatient discharge diagnosis for an NPS condition within 30 days of treatment initiation

ED=emergency department; NRT=nicotine replacement therapy; UK=United Kingdom; US=United States; DoD=Department of Defense.

The first 3 of these studies were published in peer reviewed journals.[150,151,152] The unpublished study conducted by the Department of Veterans Affairs was previously posted on the FDA web site.[153]

The results of these 4 studies are summarized in Table 37.

Table 37. Summary of Primary Results from Four Population-Based Observational Cohort Studies with Comparators

Endpoint	Author	Varenicline # Events/ Sample Size	Comparator # Events/ Sample Size	Hazard Ratio	95% CI	
					Lower Limit	Upper Limit
Fatal Or Non Fatal Self Harm	Thomas	19 / 30,352	69 / 78,407	0.88	0.52	1.49
Pharmacological Treatment For Depression	Thomas	255 / 18,386	799 / 42,475	0.75	0.65	0.87

Table 37. Summary of Primary Results from Four Population-Based Observational Cohort Studies with Comparators

Endpoint	Author	Varenicline # Events/ Sample Size	Comparator # Events/ Sample Size	Hazard Ratio	95% CI	
					Lower Limit	Upper Limit
Hospitalized For Neuropsychiatric Condition	Meyer	16 / 10,814	14 / 10,814	1.14	0.56	2.34
	Department of Veterans Affairs	16 / 14,131	21 / 14,131	0.76	0.40	1.46
	Pasternak[a]	39 / 17,935	46 / 17,935	0.85	0.55	1.30

a. Includes hospitalizations and also emergency department visits for NPS conditions.

Subsequent Observational Studies

Detailed discussions of the 3 subsequent observational studies are provided below.

Molero Y, Lichtenstein P, Zetterquist J, Gumpert CH, Fazel S. Varenicline and risk of psychiatric conditions, suicidal behaviour, criminal offending, and transport accidents and offences: population based cohort study. BMJ 2015;350:h2388.[154]

Design: This population based cohort study collected information on individuals aged 15 and older using the Swedish national registers. The study subjects were individuals treated with varenicline during the study period (22 November 2006 to 31 December 2009). Each study subject served as his/her own control; time during varenicline treatment (12 weeks from the date of the first collected prescription) was compared to time while not treated with varenicline.

Outcomes: Incident psychiatric conditions were defined as hospital admissions and outpatient visits in specialized care for psychoses, mood conditions and anxiety conditions. Suicidal behavior was defined as emergency inpatient or outpatient hospital visits or death due to intentional self-harm. Convictions and suspected crimes were examined separately for all offences in the penal code, except traffic offences. Transport accidents were defined as emergency inpatient or outpatient hospital visits or death due to transport accidents. Traffic offences were defined as convictions or suspicions of traffic offences.

Results: Among the total population of Sweden aged 15 and older (n=7,917,436), the study identified 69,757 individuals treated with varenicline during the study period. Cox proportional hazards regression was used to estimate hazard ratios (HRs) that compared the risk of an outcome for an individual while treated with varenicline relative to the risk for the same individual when not treated with varenicline. The study found no evidence that varenicline treatment was associated with an increased risk of suicidal behavior, conviction for or suspicion of criminal offences, transport accidents, or conviction for or suspicion of traffic offences. Among those with pre-existing psychiatric disorders, varenicline treatment

was associated with an increased risk of incident anxiety conditions (HR=1.23; 95%CI:1.01-1.51) and incident mood conditions (HR=1.31; 95%CI:1.06-1.63) but not incident psychoses. Among those with no pre-existing psychiatric disorders, varenicline treatment was not associated with an increased risk of any of the three incident psychiatric conditions studied.

Authors Conclusions: When we compared periods of varenicline treatment with periods of non-treatment within the same person to control for confounding by indication, we found no associations with suicidal behavior, suspected and convicted criminal offending, transport accidents, or suspected and convicted traffic offences. Varenicline treatment was associated with a small increase in the risk of incident anxiety conditions and mood conditions, although the risk increase was limited to people with pre-existing psychiatric conditions.

Strengths and Limitations: The major limitation identified by the authors was the within person analyses did not take time varying confounders into account – that is, factors that were associated with both smoking cessation attempt and the outcome. The increased risk of mood and anxiety conditions during varenicline treatment in this group could thus be caused by time varying factors other than varenicline. Therefore they should be regarded with caution and need to be confirmed in further studies.

Other limitations included the use of official registers, which underestimate true rates of most outcomes; only outcomes serious enough to warrant emergency visits or hospital admission (for psychiatric conditions, transport accidents, or suicidal behaviours) or detection by the police (for crime outcomes), would end up in the registers. The prescription data is unable to account for the lack of or variations in adherence. The study was conducted in Sweden, a country with a relatively low prevalence of daily smokers in international comparisons.

Among the strengths of this study, it improved on previous observational studies through the use of a within person design that adjusts for both residual confounders and confounding by indication. It extends the findings of randomized controlled clinical trials by examining associations in a large population based cohort sufficiently powered to detect rare events, by studying a wide range of adverse outcomes, and by separately examining people with pre-existing psychiatric diagnoses.

Kotz D, Viechtbauer W, Simpson C, van Schayck OCP, West R, Sheikh A. Cardiovascular and neuropsychiatric risks of varenicline: a retrospective cohort study. Lancet Respir Med 2015 Oct;3(10):761-8. doi: 10.1016/S2213-2600(15)00320-3.[155]

Design: This is a population-based cohort study of patients from the validated QResearch database, which holds data from 753 National Health Service general practices across England. The study identified patients aged 18-100 years who received a prescription for varenicline, bupropion or NRT between January 1, 2007 and June 30, 2012. The date of first prescription determined entry date to the cohort. Patients were followed for 6 months to compare incident neuropsychiatric and cardiovascular events. Patients were excluded if they had used one of the drugs during the 12 months before the study start date or received a prescription of a combination of these drugs during the 6 month follow-up period.

Outcomes: The incident cardiovascular events of interest were ischaemic heart disease, cerebral infarction and haemorrhage, heart failure, peripheral vascular disease, and cardiac arrhythmia. The incident neuropsychiatric events of interest were depression and fatal or non-fatal intentional self-harm.

Results: There were 51,450 varenicline users, 6,557 bupropion users and 106,759 NRT users. Cox proportional hazards regression models, adjusted for potential confounders (e.g., age, sex, socioeconomic status, relevant comorbidities, and alcohol misuse) were used to estimate hazard ratios for varenicline users compared to NRT users. Any recordings of the neuropsychiatric and cardiovascular events of interest that occurred before the patient's entry date to the cohort were also included as potential confounders. Varenicline users were less likely than NRT users to experience incident depression (HR=0.66; 95%CI:0.63-0.69) and self-harm (HR=0.56; 95%CI:0.46-0.68). Varenicline users were also less likely to experience any of the incident cardiovascular events, with the exception of peripheral vascular disease (HR=0.82; 95%CI:0.67-1.01). Propensity score matched analyses with trimming were conducted, to control for potential confounding by indication, and found no evidence of increased risk of any neuropsychiatric or cardiovascular event when varenicline was compared with NRT.

Authors Conclusions: We found no evidence of any increased risk of neuropsychiatric or cardiovascular adverse events in smokers using varenicline or bupropion when compared with NRT users. On the contrary, some events were associated with a reduced risk, including the events with the highest noted incidences (i.e., depression and ischaemic heart disease).

Strengths and Limitations: The major strength of this study identified by authors is that this is the largest original study ever done of this topic. They also note that the study investigated multiple neuropsychiatric and cardiovascular adverse events with the same methods. Third, a major advantage of use of a large general practice database is generalizability of findings from compared with randomized controlled trials because almost all individuals living in the United Kingdom are registered with a general practice and have free and ready access to smoking cessation treatment, irrespective of their socioeconomic status. They note a final strength is they published the study protocol in a peer-reviewed journal before they began analysis.[156]

The authors identified several limitations, most of which relate to the observational study design. There were large differences in patient characteristics at baseline. NRT users were older and more socioeconomically deprived and showed a higher prevalence of all of the neuropsychiatric and cardiovascular risk factors being studies and the comorbid diseases controlled for as confounders. Although differences in these measured confounders were balanced in the statistical analyses, the authors performed additional analyses to model whether potential unmeasured confounders could reasonably reverse the study conclusions. They set the combined HR of unmeasured confounders at 3, which is equivalent to the risk of premature death for current vs never smokers. The results of this modelling showed that, for any of the neuropsychiatric and cardiovascular events studied, the prevalence of the unmeasured confounders would need to be at least 20% higher in the NRT group than in the varenicline group for the conclusions to be false. However, a limitation of the modelling

approach is that it assumes the unmeasured confounder is not associated with other confounders within the exposure group.

A second limitation identified by the authors was the use of routinely collected data, some of which might have been incomplete or inaccurate. They note that this concern is mitigated by the fact that the QResearch database has been validated for answering research questions such as the one examined in this study. However, some variables of potential interest, including drug adherence and previous or present levels of tobacco exposure, were not available. They also note that they did not measure what the FDA has described as "nuanced" neuropsychiatric symptoms that are difficult to classify or that involved aggression. Such symptoms probably cannot be addressed with patient records and need specific monitoring in studies with primary data collection. Finally, they note that they did not link their dataset to other datasets to assess mortality because fatalities would usually be recorded in this general practitioner dataset within a month.

Cunningham FE, Hur K, Dong D, Miller DR, Zhang R, Wei X, McCarren M, Mosholder AD, Graham DJ, Aspinall SL, Good CB. A comparison of neuropsychiatric adverse events during early treatment with varenicline or a nicotine patch. Addiction 2016; 111:1283–1292. doi: 10.1111/add.13329.[58]

Design: This study was conducted in patients served by the US Department of Veterans Affairs (VA) using national information maintained in automated, linked databases which contain information on VA medical encounters, including in-patient hospitalizations, out-patient visits and emergency department visits, diagnoses, procedures, patient demographics, mortality and prescriptions filled in the VA. Subjects were VA patients with a prescription for varenicline or the nicotine patch (NP) between May 1, 2006 and September 30, 2007, a period prior to national warnings of potential adverse events associated with varenicline. The index date was defined as the date of initial prescription. Follow-up began on the index date and continued until 30 days after the index date, an outcome event occurred, the patient died, or the end of the study period, whichever came first. Study patients were restricted to those with ongoing contact with the VA healthcare system and excluded those with a VA prescription for varenicline or NP in the 12 months prior to the index date.

Outcomes: The primary outcome was in-patient hospitalizations with a primary discharge diagnosis of a mental health disorder, defined as depression, schizophrenia, bipolar disorder, suicide attempt, post-traumatic stress disorder (PTSD), other psychosis, and drug-induced mental disorders. The secondary outcome was new-onset or exacerbation of the same mental health disorders in an out-patient setting.

Results: A retrospective new user cohort analysis comparing varenicline to NP was conducted. There were 15,255 varenicline- and 123,054 NP-treated patients during the study period. Patients initiating varenicline were propensity score-matched to patients starting NP using a 1:2 ratio to control for potential confounding. A successful propensity score match was obtained for 11,774 varenicline-treated patients. The primary analysis was conducted on the matched data using Cox proportional regression models to estimate HRs with 95% CIs. There were no hospitalizations for suicide attempts in either treatment arm and the HRs for hospitalization for the other 6 disorders were not increased in the varenicline group compared

with the NP group during the follow-up period. There were no differences in the risks for out-patient clinic visits for any of the disorders between the varenicline and NP treatment groups, except for schizophrenia (HR=1.27; 95%CI:1.07-1.51). Only a few statistically significant interactions between the underlying mental health of the patients and treatment group were found in the models. Further analyses were conducted to investigate these significant interactions by performing a 1:2 propensity score match separately for patients with no history of mental health disorder (NMD) and patients with a history of severe mental health disorder (SMD). Cox regression analyses conducted on the matched subgroups revealed there was a significant difference in out-patient clinic visits for schizophrenia between varenicline and NP in the SMD subgroup (HR=1.40; 95%CI:1.09-1.80).

Authors Conclusions: We found no differences in the risks of hospitalization for mental health disorders with varenicline compared to NP in the primary analysis. However, the rate of out-patient clinic visits with a primary diagnosis of schizophrenia was increased significantly among VA patients who received varenicline, the increase being evident only in those with a pre-existing mental health disorder. This may reflect a worsening of symptoms, to the point that patients required more out-patient appointments but not an admission. Nevertheless, other explanations are possible (eg, closer monitoring during a smoking cessation attempt).

Strengths and Limitations: The authors identify the major strength of this study as its use of real world observational data in veterans who were treated with varenicline prior to accounts of severe neuropsychiatric adverse events, which precludes a potential reporting bias related to the safety of varenicline. An additional strength is its use of propensity score-matching to adjust for potential confounding by indication. Finally, despite the limited time period of the study, it includes more than 10,000 patients exposed to varenicline.

Among its limitations, the authors cite its reliance upon administrative data obtained for VA care alone. These data did not contain information on hospital stays and clinic visits outside the VA health-care system. Secondly, the study was not able to assess rare outcomes such as suicidality reliably, and many patients experiencing suicidal ideation or behavior may not seek medical attention. In addition, common neuropsychiatric adverse effects such as anxiety and depression can be difficult to identify using electronic health records because the patients are unlikely to be hospitalized and may not even be seen as out-patients. Manifestations of PTSD such as insomnia, nightmares or sleep disturbances are difficult to identify using ICD-9 codes and administrative data. Thirdly, the study does not account for nicotine withdrawal symptoms and had no data on smoking cessation rates. An association between smoking abstinence and serious neuropsychiatric adverse effects could affect the interpretation of results. Fourthly, even with propensity score-matching, it is still possible that residual confounding may be present due to unknown or unmeasured confounding factors. Further, nicotine patches are also sold over-the-counter so we cannot be sure that the NP group represented a true new user cohort

[150] Thomas KH, Martin RM, Davies NM, et al. Smoking cessation treatment and risk of depression, suicide, and self harm in the Clinical Practice Research Datalink: prospective cohort study. BMJ 2013;347:f5704.

[151] Pasternak B, Svanström H, Hviid A. Use of varenicline versus bupropion and risk of psychiatric adverse events. Addiction 2013;108: 1336–43. doi: 10.1111/add.12165

[152] Meyer, TE, Taylor, LG, Xie, S, et al. Neuropsychiatric events in varenicline and nicotine replacement patch users in the Military Health System. Addiction, 2013; 108:203–10. doi: 10.1111/j.1360-0443.2012.04024.x

[153] US Department of Veterans Affairs
http://www.fda.gov/Drugs/DrugSafety/ucm276737.htm#sa

[154] Molero Y, Lichtenstein P, Zetterquist J, Gumpert CH, Fazel S. Varenicline and risk of psychiatric conditions, suicidal behaviour, criminal offending, and transport accidents and offences: population based cohort study. BMJ 2015;350:h2388.

[155] Kotz D, Viechtbauer W, Simpson C, van Schayck OCP, West R, Sheikh A. Cardiovascular and neuropsychiatric risks of varenicline: a retrospective cohort study. Lancet Respir Med 2015 Oct;3(10):761-8. doi: 10.1016/S2213-2600(15)00320-3.

[156] Kotz D, Simpson C, Viechtbauer W, van Schayck OCP, West R, Sheikh A. Cardiovascular and neuropsychiatric safety of varenicline and bupropion compared with nicotine replacement therapy for smoking cessation: study protocol of a retrospective cohort study using the QResearch general practice database. BMJ Open 2014;4:8 e005281 doi:10.1136/bmjopen-2014-005281